Achievements and Future Perspectives in the Treatment of Multisystem Langerhans Cell Histiocytosis

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Clinical stratification and response evaluation

The ignorance of the pathogenesis and the failure to establish generally accepted diagnostic criteria have inhibited the development of a rational treatment policy for multisystem LCH. The therapy for LCH, therefore, has varied over the past century according to what was believed to be the cause of the disease. Only with the introduction of new concepts of staging and diagnostic criteria it became possible to collect large enough numbers of patients to carry out prospective clinical trials. Empirically it has been shown that the treatment of LCH should depend on the extent of the disease, and patients were stratified as having “single system” disease (bone, skin, lymphnode, lung, or CNS) with single site and multi site involvement, and “multisystem” disease, often associated with dysfunction of the so called “risk organs”, i.e. liver, lungs, spleen or hematopoietic system.

As the disease may follow different natural courses a new definition and assessment of response to a given treatment had to be established. The following criteria were defined by the Histiocyte Society in 1990:

- complete resolution of the disease (no active disease, NAD),
- disease regression (active disease, AD-better),
- intermediate response with regression of some and reappearance of other lesions (AD-intermediate, mixed) or unchanged disease (AD-intermediate, stable), and
- progression of the disease (AD-worse)

Prospective clinical trials in multisystem disease (MS)

Two major approaches existed throughout the last twenty years for the therapy of multisystem disease. They included a conservative approach (single center study) with treatment used only during disease exacerbation, and an approach with intensive chemotherapy induction followed by continuation treatment (carried out by two large cooperative clinical trials: the Italian AIEOP-CNR-HX 83 study and the German/Austrian DAL-HX 83/90 study). Despite different strategies, the overall mortality was about 20% in both therapy approaches. In contrast, the incidence of disease-related permanent consequences (late sequelae) was 67% in the conservative treatment study and only 33% in the DAL-HX studies. The comparison of the study results evidenced a lower incidence of disease reactivations in the DAL-HX studies (overall 23%) indicating that effective treatment may beneficially influence the natural course of the disease.

In the first international randomized chemotherapy trial LCH I, initiated by the Histiocyte Society in 1991, the efficacy of monotherapy with vinblastine and etoposide regarding the course of disease and outcome was compared in a randomized way. No significant difference was found with respect to early and late response to treatment as well as prevention of recurrences and late sequelae. In the following international trial LCH II continuous oral prednisone combined with vinblastine with or without the addition of etoposide was compared, adopting a new stratification system to distinguish between “risk” patients with involvement of “risk organs” like liver, spleen, lungs, hematopoietic system or age under 2 years, and “low risk” patients without such organs involved and age beyond 2 years. “Risk” patients were randomized between arm A (2-drugs) and arm B (3-drugs), “low risk” patients uniformly received initial treatment according to the 2-drug arm only. All patients received continuation therapy with 6-mercaptopurine and prednisone/vinblastine pulses. The whole
treatment duration was limited to 24 weeks as it was in LCH I.

In the “low risk” group 89% of patients were responders at the week 6 evaluation, and no fatalities occurred. Among the “risk” patients, the overall response rate was superior to that in the LCH I study and similar to that of the previous DAL studies. Between arm A and B in “risk” patients, however, no statistical difference with respect to response, survival and reactivation free survival has been found. Patients with involvement of “risk organs”, who did not show disease regression by week 6 or 12 of therapy, had a poor outcome and a high rate of mortality (approximately 20%). This figure did not differ from that in the DAL and LCH I studies. Notably, all patients who died in LCH I and LCH II studies irrespectively of age had at least one “risk organ” involved at diagnosis. It seems justified, therefore, to regard “risk organ” involvement and response to initial treatment as the most important prognostic factors, whereas age under 2 years did not prove to be of independent prognostic importance. Consequently, non responding patients might benefit from a rapid switch to an alternative salvage treatment.

The probability of reactivation within two years after complete response (non active disease) was about 50% in both low risk and risk patients. This compared well with the results in the LCH I study, but was inferior to the results of the DAL studies, which demonstrates a potential benefit of a longer treatment duration (12 months in DAL studies vs. 6 months in LCH studies).7

In the ongoing third international randomized trial LCH III (www.histiocyte society) patients are stratified into three groups:

(1) multisystem patients with involvement of one or more risk organs (“risk” patients),

(2) multisystem patients without involvement of risk organs (“low risk” patients), and

(3) single system patients with “multifocal bone disease” or localized “special site” involvement (paranasal, parameningeal, periorbital, and mastoid region or intraspinal extension) which can lead to persisting soft tissue swelling.

These locations are considered to be risk sites for CNS disease, except surgical excision is feasible (e.g. periorbital eosinophilic granuloma).8,9 “Risk” patients after central randomisation are entered in two different treatment arms (arm A and B) which include prednisone, vinblastine and 6-mercaptopurin (6-MP) with or without methotrexate (MTX). Initial treatment consists of one or two courses depending on response and is followed by continuation therapy with 6-MP/MTX and Pred/VBL pulses (treatment duration 12 months). For “low risk” patients a standard therapy with prednisone and vinblastine is recommended with random assignment to a continuation therapy (6-MP/MTX and pulses) for 6 or 12 months. Patients with multifocal bone or special site involvement are treated with prednisone and vinblastine followed pulse therapy (Pred/VBL) (treatment duration 6 months). So far, the overall results in the two risk groups are comparable with the outcome in the LCH II study with respect to response and mortality. It is too early to communicate further more detailed information regarding the impact of MTX in arm B and treatment duration on the reactivation frequency and rate of permanent consequences.

New approaches for resistant disease

Not responding “risk” patients are considered to have a high risk of mortality (about 75%). Cyclosporin A alone and in combination with dexamethason and anti-thymocyte globulin has been suggested as an alternative treatment approach, however, especially in patients with advanced chemotherapy-resistant multisystem disease convincing data of efficacy is lacking.10,11 Also regarding the role of bone marrow transplantation only few and inconsistent data is available. Especially, myeloablative stem cell transplantation as a possible salvage approach for these patients has shown to be associated with a high risk of transplant-related mortality (45%). Therefore, allogeneic stem cell transplantation following a reduced intensity conditioning regimen (RIC-SCT) has been performed recently, as an alternative salvage approach with promising preliminary results. Seven out of nine patients with persistent risk organ involvement survived and were in good clinical condition after a median follow-up of 390 days post transplantation.12 Notably, even in
those patients who responded well to RIC-SCT, clinical recovery from the underlying disease after transplantation was slow and protracted, reflecting a slow and gradual decrease of cytokine load and related symptoms, which seem to be a peculiarity for this disease. These data underline the potential utility of RIC-SCT for LCH patients with resistant “risk organ” involvement.

The use of 2-chlorodeoxyadenosine (2-CDA) has recently appeared to be successful in refractory LCH.13 According to the (recently closed) salvage treatment protocol of the Histiocyte Society, 2-CDA was given as a monotherapy (5 mg/m2 2-CDA daily for 5 days at 3-4 weekly intervals; 2, 4 or 6 courses) to non-responding multisystem patients or patients with recurrent disease. The overall response rate was disappointing in therapy-resistant high risk patients. However, patients with recurrent disease manifestations in non-risk organs showed a similar good response rate as those who obtained standard Pred/VBL combination, but the risk of disease reactivation after stopping therapy was equally high as it was with standard therapy. Recently, the results of a pilot study of 2-CDA and Ara-C combined chemotherapy were published by the French LCH Study Group.14 Ten children with refractory LCH and severe hematological dysfunction, median age of 0.5 years at diagnosis, received at least 2 courses of ARA-C (1000 mg/m2/d) and 2-CDA (9mg/m2/d) administered during 5 days every 4 weeks. Seven out of these very high risk patients survived with resolution of disease after a median follow-up of 2.8 years. The encouraging results of this study together with the new experiences with RIC-SCT are a matter of debate and consideration within the Histiocyte Society for further investigation in a prospective way.

Other studies have reported success in the treatment of LCH with interferon-α, thalidomide, anti-CD1a, and tumor necrosis factor-α antibodies.2,15,16 Anecdotal experience has been published recently, regarding the use of imatinib mesylate and cladribine in CNS disease.17,18 Each of these approaches clearly needs to be evaluated prospectively before they can be recommended as standard for non-responsive MS-LCH.

How recurrences can be prevented?
A major problem in the treatment of MS-LCH is the prevention of recurrences. The probability of reactivation within two years after complete response (non active disease with resolution of all symptoms and signs) is in the range of 50% in both “low risk” and “risk” groups of the LCH I and LCH II studies. In both of these studies the treatment duration was only 6 months. Interestingly, in the DAL studies after one year therapy the reactivation rate was lower, suggesting a potential benefit of longer treatment.7 Reactivation presents usually with bone and/or skin involvement and can easily be controlled by standard therapy. A recurrence in “risk organs” after NAD is only rarely observed. Many attempts have been undertaken to find a strategy to prevent reactivations. This objective is going to be addressed by the LCH III study with the prolongation of the whole treatment period to 12 months in “risk” patients, and a randomized assignment of patients with “low risk” features to a 6 and 12 months therapy, respectively. The first reactivation mostly occurs after stopping therapy until 2 - 3 years later. Further reactivations may be seen within the same time period as after first line therapy in approximately one third of children, declining from year to year. In a cohort of 563 patients with LCH the reactivation frequency vanished after 5 years of follow-up to nearly zero, which indicates that the disease is self-limited (unpublished results of the LCH studies, Vienna). So far, no difference has been seen also after second line therapy with 2-CDA or other drugs.

The Salvage Therapy Study Group is trying hard to set up an appropriate treatment protocol for patients with recurrent disease and is looking for broad cooperation.

References


