LANGERHANS CELL HISTIOCYTOSIS

Histiocyte Society

Evaluation and Treatment Guidelines

April 2009

Contributors:

Milen Minkov	**Vienna, Austria**
Nicole Grois	**Vienna, Austria**
Kenneth McClain	**Houston, USA**
Vasanta Nanduri	**Watford, UK**
Carlos Rodriguez-Galindo	**Memphis, USA**
Ingrid Simonitsch-Klupp	**Vienna, Austria**
Johann Visser	**Leicester, UK**
Sheila Weitzman	**Toronto, Canada**
James Whitlock	**Nashville, USA**
Kevin Windebank	**Newcastle upon Tyne, UK**

Disclaimer:

These clinical guidelines have been developed by expert members of the Histiocyte Society and are intended to provide an overview of currently recommended treatment strategies for LCH. The usage and application of these clinical guidelines will take place at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions.

The following recommendations are based on current best practices in the treatment of LCH and are not necessarily based on strategies that will be used in any upcoming clinical trials. The Histiocyte Society does not sponsor, nor does it provide financial support for, the treatment detailed herein.

Table of Contents

INTRODUCTION

There are no international studies for newly diagnosed patients with Langerhans cell histiocytosis (LCH) currently open. The guidelines detailed herein have been developed for use as recommended practices in the evaluation and treatment of patients who are not formally enrolled in clinical trials, such as the upcoming LCH IV study. These guidelines are based on the best currently known treatment approaches; and take into consideration the preliminary results of the LCH-III trial.

The Histiocyte Society protocols LCH-S-2005 (salvage therapy for patients with severe disease, Chair: J. Donadieu) and LCH-HCT-2006 (stem cell transplantation after Reduced Intensity Conditioning, Chair: K.S. Baker) are currently open for enrollment.

DIAGNOSTIC CRITERIA

The diagnosis of LCH is based on histological and immunophenotypic examination of lesional tissue. The main feature is the morphologic identification of the characteristic LCH cells. Additionally, positive staining of the lesional cells with CD1a and/or Langerin (CD207) is required for definitive diagnosis (1-3). It has been demonstrated that the expression of Langerin confirms the presence of Birbeck granules (4). Because of this finding, the ultrastructural demonstration of the presence of cytoplasmic Birbeck granules (the previous diagnostic “gold standard”) is no longer necessary. Only in the case of isolated vertebra plana without a soft tissue component does the risk of biopsy outweigh the need for a tissue diagnosis. This is also true for an isolated involvement of the odontoid peg. In such a case, the patient should be closely observed to exclude a malignancy. Curettage of the center of a bone lesion is usually sufficient for pathologic diagnosis and also may trigger the injitiation of a healing process. Complete excision of bone lesions is not indicated and may increase the size of the bony defect, the time to healing, and result in late skeletal morbidity.

PRETREATMENT CLINICAL EVALUATION

1. COMPLETE HISTORY:

A complete history should include special reference to the nature and duration of symptoms. Specific symptoms to be included in the complete history are: pain, swelling, skin rashes, otorrhea, irritability, fever, loss of appetite, diarrhea, weight loss

or poor weight gain, growth failure, polydipsia, polyuria, changes in activity level, dyspnea, smoke exposure, and behavioral and neurological changes.

2. COMPLETE PHYSICAL EXAMINATION:

A complete physical examination should include measurement of temperature, height, and weight. Special attention should be paid to: pubertal status (Tanner staging), characterization of skin and scalp rashes, presence of jaundice, pallor, edema, lymphadenopathy, ear discharge, orbital abnormalities, gum and palatal lesions, dentition, soft tissue swelling, lesions on the genital and anal mucosa, tachypnea, intercostal retractions, ascites, and liver and spleen size. Specific tests should be conducted for: neurological evaluation, cranial nerve abnormalities, loss of tendon reflexes, visual deficits, and cerebellar dysfunction. This complete clinical evaluation should be performed at each follow-up visit.

3. LABORATORY AND RADIOGRAPHIC EVALUATION:

Table 1: Recommended baseline evaluation upon diagnosis and reactivation

Full blood count:
- hemoglobin, white blood cell and differential count, platelet count

Blood chemistry:
- total protein, albumin, bilirubin, ALT(SGPT), AST(SGOT), alkaline phosphatase, γGT
- BUN, creatinine, electrolytes
- Ferritin

Coagulation studies:
- INR/PT, APTT/PTT, fibrinogen

Early morning urine sample:
- Specific gravity and osmolality

Abdominal ultrasound:
- Size and structure of liver and spleen

Chest radiograph (CXR)

Skeletal radiograph survey*

* Functional imaging such as bone scan is optional and can be performed in addition to skeletal survey. PET scan has proven to be the most sensitive functional test used in the identification of LCH lesions and in evaluating patient response to therapy. However, PET scan is currently expensive and not widely available (Philips et al, 2009)

Table 2: Laboratory investigations, imaging and specialized clinical assessments recommended for specific clinical scenarios

Indication	Assessment / test
Bicytopenia, pancytopenia, or persistent unexplained single cytopenia	• Bone marrow aspirate & trephine biopsy to exclude causes other than LCH
Liver dysfunction	• Liver biopsy only recommended if there is clinically significant liver involvement and the result will alter treatment (i.e. to differentiate between active LCH and sclerosing cholangitis)
Lung involvement (abnormal CXR or symptoms/signs suggestive for lung involvement) **Abnormal lung CT AND findings not characteristic for LCH or suspicion for atypical infection**	• Lung high resolution computed tomography (HR-CT) or preferably low dose multi-detector HR-CT if available • Lung function test (if age appropriate) • Bronchoalveolar lavage (BAL): >5% CD1a-positive cells in BAL fluid is diagnostic in non-smokers • Lung biopsy (if BAL is not diagnostic)
Suspected craniofacial bone lesions including maxilla and mandible	• MRI of head*
Suspected vertebral lesions	• MRI of spine (to exclude spinal cord compression)
Visual or neurological abnormalities	• MRI of head* • Neurology assessment • Neuropsychometric assessment
Suspected endocrine abnormality (i.e. short stature, growth failure, polyuria, polydipsia, hypothalamic syndromes, precocious or delayed puberty)	• Endocrine assessment (including water deprivation test and dynamic tests of the anterior pituitary and thyroid) • MRI of head*
Aural discharge or suspected hearing impairment/mastoid involvement	• Formal hearing assessment • MRI of head* • HR-CT of temporal bone
Unexplained chronic diarrhea, failure to thrive, or evidence of malabsorption	• Endoscopy and biopsy

*MRI of head should include the brain, hypothalamus - pituitary axis and all craniofacial bones. The use of intravenous contrast (Gadolinium – DTPA) is mandatory.

DEFINITION OF ORGAN INVOLVEMENT

Risk organs (RO)

Hematopoietic involvement: (with or without bone marrow involvement*)	**At least 2 of the following:** • **anemia:** hemoglobin <10 g/dl, infants <9 g/dl (not due to other causes; e.g. iron deficiency) • **leukocytopenia:** leukocytes <4,0 x 10^9/l, • **thrombocytopenia:** platelets < 100 x 10^9/l
Spleen involvement:	• **enlargement** > 2 cm below costal margin in the midclavicular line
Liver involvement:	• **enlargement** > 3 cm below costal margin in the midclavicular line and/or • liver **dysfunction** (i.e. hypoproteinemia <55g/l, hypoalbuminemia <25g/l not due to other causes) and/or • **histopathological** diagnosis
Lung involvement:	• typical changes on **HR-CT** (low dose multi-detector CT if available) and/or • **histopathological** / **cytological** diagnosis

*Bone marrow involvement is defined as demonstration of CD1a positive cells on bone marrow smears. The clinical significance of CD1a positivity in the bone marrow remains to be proven. Hemophagocytosis may be prominent in severe progressive cases.

"Special Sites" – In certain situations, such as odontoid peg and vertebral lesions with intraspinal soft tissue extension, lesions are located in functionally critical anatomical sites. Lesions located in these sites may cause immediate risk to the patient because of the potential for disease progression and the hazards of attempting local therapy. These lesions are considered disease in a "Special Site." Isolated disease in a Special Site may justify systemic therapy.

Vertebral lesions without soft tissue extension, e.g. vertebra plana, are not regarded as "Special Site" lesions.

“Craniofacial bone involvement” - lesions in the orbital, temporal, mastoid, sphenoidal, zygomatic, or ethmoidal bones; the maxilla or paranasal sinuses; or cranial fossa; with intracranial soft tissue extension

‘‘Eye’’ involvement - proptosis, exophthalmos, or lesions in the orbits; zygomatic or sphenoidal bone

‘‘Ear’’ involvement - external otitis, otitis media, otorrhea; or lesions in the temporal bone, mastoid, or petrous bone

‘‘Oral’’ involvement - lesions in the oral mucosa, gums, palatal bone, maxilla, and mandible

“CNS Risk Lesions”

Recent knowledge suggests that prolonged involvement of skull bones (excluding those in the vault) predisposes patients to the development of DI (5). In this study, patients with MS-LCH and "craniofacial involvement" – particularly those with involvement of the ‘‘ear,’’ ‘‘eye,’’ and the "oral" sites at diagnosis – carried a significantly increased risk to develop DI during their course. In a bivariate model adjusted for the extent of disease (MS-LCH vs. SS-LCH), the authors found that the influence of lesions in **‘‘ears’’** (RHR 1.8, P1/40.005), **‘‘eyes’’** (RHR 1.7; P1/40.024), and **‘‘oral cavity’’** (RHR1.8; P1/4 0.007), and combined "**craniofacial lesions**" (RHR 1.6; P1/40.030) is statistically significant. This risk is augmented when the disease remains active for a longer period of time or reactivates (5).

STRATIFICATION

Depending on the extent and localisation of the disease at the time of evaluation, the following clinical categories have been defined:

Clinical classification of LCH:

Single System LCH (SS-LCH)	**One organ/system involved (uni- or multifocal):** • Bone: unifocal (single bone) or multifocal (>1 bone) • Skin • Lymph node (not the draining lymph node of another LCH lesion) • Lungs • Hypothalamic-pituitary / Central nervous system • Other (e.g. thyroid, thymus)
Multisystem LCH (MS-LCH)	**Two or more organs/systems involved** With or without involvement of "Risk Organs"

The following localisations and disease extent categories are considered indications for systemic therapy:

- **SS-LCH with "CNS-risk" lesions**
- **SS-LCH with multifocal bone lesions (MFB)**
- **SS-LCH with "special site" lesions**
- **MS-LCH with/without involvement of "risk organs"**

TREATMENT

Treating physicians participating in clinical trials of the Histiocyte Society are encouraged to formally enroll their patients on these protocols after obtaining the approval of their institution's ethical board. By enrolling their patients on these protocols, physicians will help to advance knowledge about the biology and treatment of LCH. The Histiocyte Society intends for the recommendations provided below to serve as physician guidelines in the management of patients who are unwilling or unable to be treated on, or enrolled in, such a protocol. In order for patients to be treated on a research protocol, they must first indicate their agreement to participate in the study by providing their informed consent. It is ethically unsound, and strongly discouraged, for physicians to treat patients who have not provided their informed consent on a research protocol.

1. GENERAL CONSIDERATIONS:

- Recent evidence (unpublished preliminary data of the LCH-III Trial of the Histiocyte Society) suggests that treatment duration of 12 months reduces the rate of reactivation as compared to 6 months of total treatment. Patients with MS-LCH at diagnosis can have a variable clinical course. Those without involvement of risk organs, as well as those with involvement of risk organs who respond to standard initial therapy, have an excellent chance of long-term survival. A combination of prednisone (PRED) and vinblastine (VBL) has been proven to be effective treatment with minimal toxicity (6-8) and is therefore the standard initial therapy for all patients in whom systemic therapy is indicated. Patients with risk organ involvement who do not respond within the first 6 weeks of therapy – especially those with evident clinical progression – have an unfavourable prognosis (7, 9,10). For such patients, early therapy intensification is justified.
- Patients with MFB are known to have an excellent prognosis (survival of 100%), but have a high tendency for disease reactivation (30-50%) and permanent consequences. The same is true for patients with “special site” and “CNS-risk” lesions. There is a 40% likelihood that these patients will develop diabetes insipidus and other endocrinopathies; as well as parenchymal brain disease. There is greatest risk of parenchymal brain disease developing in the basal ganglia and cerebellum. Therapy is to be used in these groups for the purpose of preventing reactivations, permanent consequences and disabilities. However, evidence to support different regimens is limited and is mainly based on retrospective analyses (11) and expert opinion.

2. FIRST LINE TREATMENT

2.1. Multisystem Disease

An initial 6-week course of therapy with vinblastine and prednisone **(Figure 1)** is suggested for all patients with MS-LCH; regardless of risk organ involvement. Further therapy depends on patient response to initial therapy. In order to determine response to initial therapy, assessment at the end of the initial 6 week course of therapy is necessary.

Patients found to have RO involvement at diagnosis and who have not demonstrated improvement in risk organs are candidates for salvage therapy options (see below).

The same is recommended for patients who were not found to have RO involvement at diagnosis, but developed RO disease while on therapy.
For patients without RO involvement who have not shown improvement (e.g. AD intermediate), and for patients with RO involvement at diagnosis who have responded to the initial course (e.g. AD better), a second course of treatment with vinblastine and prednisone (Figure 2) is recommended.
It is also recommended that all patients who have complete disease resolution (NAD) after 6-12 weeks of initial therapy continue with maintenance therapy. Maintenance therapy consists of pulses of vinblastine and prednisone every 3 weeks and daily continuous 6-mercaptopurine (6MP) for a total treatment duration of 12 months (Figure 3).

It is recommended that patients who continue to experience involvement of risk organs after initial course 2 (12 weeks of therapy) are switched to salvage therapy. It is also recommended that patients without risk organ involvement who do not demonstrate improvement after course 2 be administered another course of therapy with alternative drugs (see “Second-line therapy for non-risk LCH” below)

2.2. Multifocal bone (MFB), “special site” and “CNS-risk” lesions

At the present time, there is no conclusive evidence to support an optimal course of treatment for use with these patient subgroups. The rationale for systemic treatment is the considerable risk of permanent consequences and disabilities that may adversely affect individuals’ quality of life. Data from the DAL-HX 83 and DAL-HX 90 non-randomized prospective trials indicates that 1 year of systemic treatment with vinblastine, prednisone, and 6-mercaptopurine has the potential to reduce both the reactivation rate and the frequency of permanent consequences when compared to historical controls (11). Based upon this data, the Histiocyte Society recommends systemic therapy, consisting of course 1 **(Figure 1)** ± course 2 **(Figure 2)**; and a continuation therapy with PRED/VBL pulses every 3 weeks. The total recommended duration of treatment is 12 months (as in Figure 3 but without 6MP).

3. SECOND LINE TREATMENT

3.1. Salvage therapy options for Risk patients:

Currently, there is insufficient evidence to support an optimal course of treatment for use with patients suffering from severe progressive MS-LCH who do not respond to standard therapy. Recently, promising results have been reported for patients treated with a combined regimen of 2-chlorodeoxyadenosine (2-CdA, Cladribin, Leustatin) and cytarabine (Ara-C) (12); as well as stem cell transplantation after reduced intensity conditioning regimen (RIC-SCT) (13).

However, the results generated by both reports are based on limited observations and must be validated by the prospective clinical trials. The Histiocyte Society currently has open trials for both treatment options. For the rare cases in which salvage therapy is planned, it is recommended that you contact an LCH expert or the principal investigators of one of the aforementioned open studies.

3.2. Second-line therapy for Non-Risk patients:

Presently, optimal second-line options for patients diagnosed with persisting or relapsing LCH in non-risk organs have not yet been identified.

In the future, the Histiocyte Society will conduct a clinical trial for the purpose of identifying optimal second-line options for these patients.

Previously used treatments that have demonstrated success include the intralesional injection of steroids (14); the combination of vincristine, prednisone, and cytarabine (15); and 2-chlorodeoxyadenosine as a single agent (16-18).

4. CNS DISEASE

Treatment for patients diagnosed with CNS disease depends on the type and extent of disease and prior treatment received and thus must be determined on an individual basis.

SUPPORTIVE CARE

1. PNEUMOCYSTIS CARINII (PCP) PROPHYLAXIS

Patients receiving systemic therapy for LCH are at risk for PCP infection. Prophylaxis against PCP should be given in accordance with local standards.

2. TRANSFUSIONS OF RED CELLS AND PLATELETS

Patients receiving "salvage" therapy for LCH are at risk for transfusion-related complications, including cytomegalovirus infection and graft-*vs.*-host disease (GvHD). Blood cell components should be filtered and irradiated (> 2500 rad or 25 Gy) for prevention of GvHD.

3. G-CSF

In case of prolonged neutropenia, G-CSF may be given subcutaneously or intravenously. The use of GM-CSF is not recommended.

4. THERAPY MODIFICATIONS

Infants with body weight under 10 kg

Drug doses are calculated on body surface area (BSA) and adjusted for age as follows:

< 6 months	50% of dose calculated from BSA
> 6 months < 12 months	75% of dose calculated from BSA
> 12 months	100% of dose calculated from BSA

Bone marrow toxicity

It is recommended that an absolute neutrophil count greater than 1.0 x 10^9/l and a platelet count greater than 100 x 10^9/l be observed before each course of therapy is initiated, unless cytopenias are disease related. In the case of persistent disease activity, it is recommended that physicians consider continuing treatment regardless of the patient's hematological values.

Continuation Therapy with Oral 6-Mercaptopurine

If neutrophils fall below 1.0 x 10^9/l or platelets below 100 x 10^9/l, treatment should be stopped until recovery occurs above these levels, and then resumed as tolerated. If neutrophils fall below 0.5 x 10^9/l or platelets below 50 x 10^9/l on >2 occasions, consider discontinuation of co-trimoxazole. Pentamidine or dapsone can be used as alternative prophylaxis for PCP.

Neurotoxicity

In the event of significant toxicity (extensive weakness, severe paresthesia, severe ileus), vinblastine may be temporarily discontinued and resumed at 50% dose when toxicity resolves, with progressive increase to full dose as tolerated.

ASSESSMENT OF TREATMENT RESPONSE

In accordance with the nature of LCH, the following definitions should be applied to judge the effect of treatment:

Definition of disease state

NON ACTIVE DISEASE (NAD)	no evidence of disease	Resolution of all signs or symptoms
ACTIVE DISEASE (AD)	regressive disease	Regression of signs or symptoms, no new lesions
	stable disease	persistence of signs or symptoms, no new lesions
	progressive disease*	progression of signs or symptoms and/or appearance of new lesions

Definition of response criteria

There are three categories of response

BETTER	complete resolution	NAD
	regression	AD better
INTERMEDIATE	mixed	new lesions in one site, regression in another site
	stable	Unchanged
WORSE	progression*	

*In isolated bone disease progression is defined as appearance of new bone lesions or lesions in other organs

FOLLOW UP INVESTIGATIONS AFTER END OF THERAPY

	YEAR 1*	**YEARS 2 – 5***
Clinical examination	Every 6 weeks	Every 6 months
Height, weight, pubertal status	Every 6 months	Every 6 months
Lab-examinations in patients who have had respective organ involvement: Blood count, ESR, liver and renal function tests, urine osmolality	Every 3 months	Yearly
Radiographs of bone lesions	Only if new lesions or reactivation suspected	Only if new lesions or reactivation suspected
Audiology in patients with history of ear/mastoid involvement	At 1 year	At 5 years
HR-CT, pulmonary function tests in patients with pulmonary involvement	Every 6 months	Only if progression suspected
Ultrasound in patients with liver involvement	Every 6 months	Yearly
Brain MRI in patients with DI or other endocrinopathies or patients with CNS risk lesions	At 1year	Every 2 years
Neuropsychometric assessment in patients with CNS involvement	At 1 year	Every 2 years

*Adapt for individual patients on the basis of systems involved and clinical indications

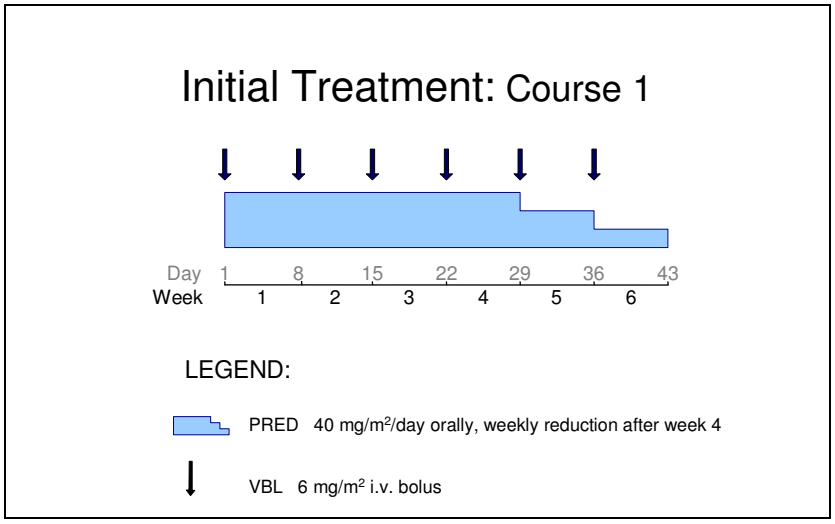

Figure 1

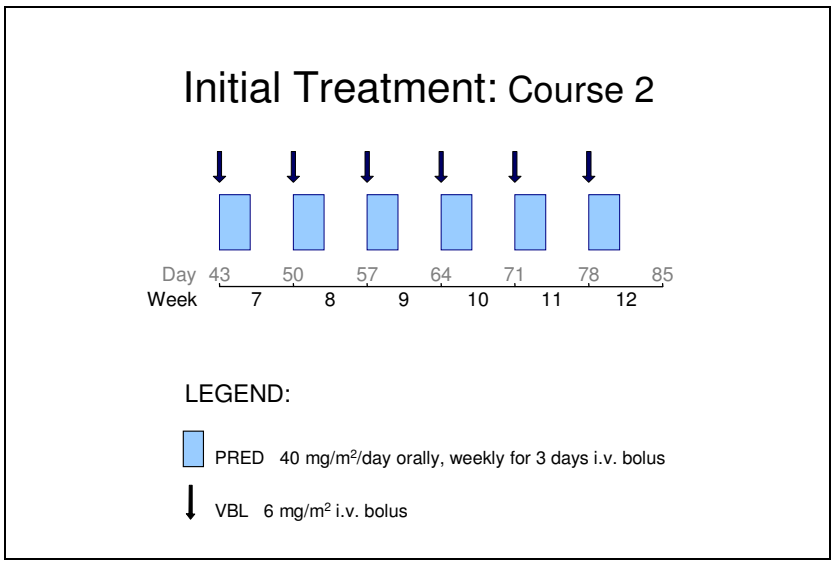

Figure 2

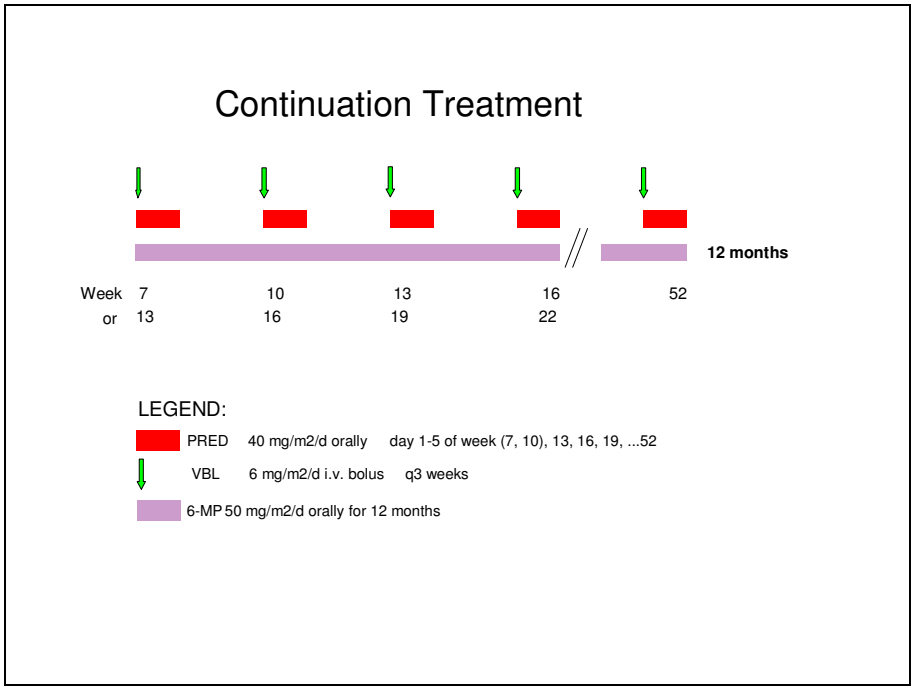
Continuation Treatment
12 months
Week 7 10 13 16 52
or 13 16 19 22
LEGEND:
PRED 40 mg/m2/d orally day 1-5 of week (7, 10), 13, 16, 19, ...52
VBL 6 mg/m2/d i.v. bolus q3 weeks
6-MP 50 mg/m2/d orally for 12 months

Figure 3

For more information please contact the principal investigators or national LCH experts:

Jean Donadieu, MD

Principal Investigator of the LCH-S-2005 Clinical Trial

Hospital Trousseau
Hematologie-Oncologie
26 Rue Du D Netter
Paris, F-75012 France
P + 33 - 1- 44736062
F + 33 – 1 - 44736573
Email: j.donadieu@invs.sante.fr

K. Scott Baker, MD, MS

Principal investigator LCH-HCT-2006 Trial

Fred Hutchinson Cancer Research Center
1100 Fairview Ave. N
Mailstop D5-283
PO Box 19024
Seattle, WA 98109-1024, USA
Phone: +1-206-667-5594
Fax: +1-206-667-5899
Email: ksbaker@fhcrc.org

Milen Minkov, MD, PhD

Chair of the Study Group "Second Line Therapy for Non-Risk Patients"

International LCH Study Reference Center
St. Anna Children's Hospital
Kinderspitalgasse 6
A-1090 Vienna
Austria
Phone: +43 1 40170 4760
Fax: +43 1 40170 7430
Email: lch@stanna.at

List of national LCH experts in USA and Canada:

Carlos Rodriguez-Galindo, MD
St. Jude Children´s Research Hospital
Department of Oncology
332 North Lauderdale
Memphis, Tennessee 38105 USA
Phone: +1 901 495 2203
Fax: +1 901 521 9005
Email: Carlos.Rodriguez-Galindo@stjude.org

James A. Whitlock, MD
Craig-Weaver Professor of Pediatrics
Director, Pediatric Hematology/Oncology
Vanderbilt University Medical Center
2220 Pierce Avenue, 397 PRB
Nashville TN 37232 USA
Phone: +1 615 936 1762
Fax: +1 615 936 1767
Email: jim.whitlock@vanderbilt.edu

Kenneth McClain MD, PhD
Texas Children's Cancer Center and Hematology Service
6701 Fannin Street CC 1500, Suite 1410
Houston TX 77030 USA
Phone: +1 832 822 4208
Fax: +1 832 825 1503
Email: klmcclain@txccc.org

Sheila Weitzman, MD
Hospital for Sick Children
University Avenue
Toronto, M5G 1X8 Ontario Canada
Phone: +1 416 813 5872
Fax: +1 416 813 5327
Email: Sheila.weitzman@sickkids.ca

References:

1. Chikwava K, Jaffe R. Langerin (CD207) staining in normal pediatric tissues, reactive lymph nodes, and childhood histiocytic disorders. Pediatr Dev Pathol 2004;7(6):607-14.
2. Lau SK, Chu PG, Weiss LM. Immunohistochemical expression of Langerin in Langerhans cell histiocytosis and non-Langerhans cell histiocytic disorders. Am J Surg Pathol 2008;32(4):615-9.
3. Jaffe R, Weiss LM, Facchetti F. Tumors derived from Langerhans cells. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2008. p. 358-60.
4. Valladeau J, Ravel O, Dezutter-Dambuyant C, Moore K, Kleijmeer M, Liu Y, et al. Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. Immunity 2000;12(1):71-81.
5. Grois N, Potschger U, Prosch H, Minkov M, Arico M, Braier J, et al. Risk factors for diabetes insipidus in langerhans cell histiocytosis. Pediatr Blood Cancer 2006;46(2):228-33.
6. Gadner H, Heitger A, Grois N, Gatterer-Menz I, Ladisch S. Treatment strategy for disseminated Langerhans cell histiocytosis. DAL HX-83 Study Group. Med Pediatr Oncol 1994;23(2):72-80.
7. Gadner H, Grois N, Potschger U, Minkov M, Arico M, Braier J, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood 2008;111(5):2556-62.
8. McClain KL. Drug therapy for the treatment of Langerhans cell histiocytosis. Expert Opin Pharmacother 2005;6(14):2435-41.
9. Minkov M, Grois N, Heitger A, Potschger U, Westermeier T, Gadner H. Response to initial treatment of multisystem Langerhans cell histiocytosis: an important prognostic indicator. Med Pediatr Oncol 2002;39(6):581-5.
10. Gadner H, Grois N, Arico M, Broadbent V, Ceci A, Jakobson A, et al. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 2001;138(5):728-34.
11. Titgemeyer C, Grois N, Minkov M, Flucher-Wolfram B, Gatterer-Menz I, Gadner H. Pattern and course of single-system disease in Langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. Med Pediatr Oncol 2001;37(2):108-14.
12. Bernard F, Thomas C, Bertrand Y, Munzer M, Landman Parker J, Ouache M, et al. Multi-centre pilot study of 2-chlorodeoxyadenosine and cytosine arabinoside combined chemotherapy in refractory Langerhans cell histiocytosis with haematological dysfunction. Eur J Cancer 2005;41(17):2682-9.
13. Steiner M, Matthes-Martin S, Attarbaschi A, Minkov M, Grois N, Unger E, et al. Improved outcome of treatment-resistant high-risk Langerhans cell histiocytosis after allogeneic stem cell transplantation with reduced-intensity conditioning. Bone Marrow Transplant 2005;36(3):215-25.
14. Egeler RM, Thompson RC, Jr., Voute PA, Nesbit ME, Jr. Intralesional infiltration of corticosteroids in localized Langerhans' cell histiocytosis. J Pediatr Orthop 1992;12(6):811-4.
15. Egeler RM, de Kraker J, Voute PA. Cytosine-arabinoside, vincristine, and prednisolone in the treatment of children with disseminated Langerhans cell histiocytosis with organ dysfunction: experience at a single institution. Med Pediatr Oncol 1993;21(4):265-70.

16. Weitzman S, Wayne AS, Arceci R, Lipton JM, Whitlock JA. Nucleoside analogues in the therapy of Langerhans cell histiocytosis: a survey of members of the histiocyte society and review of the literature. Med Pediatr Oncol 1999;33(5):476-81.
17. Stine KC, Saylors RL, Saccente S, McClain KL, Becton DL. Efficacy of continuous infusion 2-CDA (cladribine) in pediatric patients with Langerhans cell histiocytosis. Pediatr Blood Cancer 2004;43(1):81-4.
18. Stine KC, Saylors RL, Williams LL, Becton DL. 2-Chlorodeoxyadenosine (2-CDA) for the treatment of refractory or recurrent Langerhans cell histiocytosis (LCH) in pediatric patients. Med Pediatr Oncol 1997;29(4):288-92.
19. Phillips M, Allen C, Gerson P, McClain K. Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. Pediatr Blood Cancer 2009;52:97-101