STANDARD CLINICAL PRACTICE RECOMMENDATIONS FOR PEDIATRIC-ONSET LANGERHANS CELL HISTIOCYTOSIS

The ERN PaedCan received funding by the European Union's Health Programme (2014-2020), grant agreement nr. 847032.

DISCLAIMER:

These ESCP guidance documents were produced by the relevant tumour group or specialist committee as recommendations on current best practice. The ESCP guidance documents are not clinical trial protocols.

The interpretation and responsibility of the use of ESCP guidance documents lies fully with the user who retains full responsibility for the use of these guidance documents and his actions and (treatment) decisions based thereon, such as, but without limitation thereto: checking and prescribing certain doses, checking prescriptions, etc. A user should never base its decision solely on the content of these guidance documents and should always check any other relevant medical information that is available and make appropriate use of all relevant medical information.

These guidance documents have been made publicly available by SIOP Europe – the European Society of Paediatric Oncology and the European Reference Network for Paediatric Oncology (ERN PaedCan). It is the responsibility of the user who downloads these documents to make sure that:

- their use within the Paediatric Clinical Unit / Hospital is approved according to the local clinical governance procedures.
- appropriate document control measures are in place to ensure that the most up to date locally approved versions are considered.
- any anomalies or discrepancies within the documents are immediately brought to the attention of the relevant special interest group chair and the European Clinical Study Group who has developed the ESCP guidance document.

Every care has been taken whilst preparing these documents to ensure that they are free of errors. Nonetheless, SIOP Europe and ERN PaedCan cannot be held liable for possible errors or mistakes in these guidance documents, nor can SIOP Europe and ERN PaedCan be held liable for any kind of damage resulting out of the use of these guidance documents.

INTRODUCTORY PAGES

- Guidelines for diagnosis, clinical work-up, and treatment of children and adolescents with Langerhans cell histiocytosis
- Guidelines for pediatric-onset LCH
- Version 1.2, Oct 30, 2020

This document has been developed by: the European Consortium for Histiocytosis (ECHO), WP Treatment of Pediatric-onset LCH: Jean Donadieu (France), Jan-Inge Henter (Sweden), Thomas Lehrnbecher (Germany), Milen Minkov (Austria), Elena Sieni (Italy), Vassilios Papadakis (Greece), Karel Svojgr (Czech Republic), Cor van den Bos (The Netherlands), Johannes Visser (UK).

Corresponding authors: Karel Svojgr (Young SIOPE member) & Milen Minkov (President of ECHO)

Planned review date: Oct 2023

Table of contents

1. BACKGROUND AND RATIONALE

1.1 Background

Langerhans cell histiocytosis (LCH) is a heterogeneous disease, characterized by accumulation of clonal, CD1a+/CD207+ dendritic cells in various organs. LCH can affect any organ or system of the human body, but those more frequently involved are the skeleton (80% of cases), the skin (33%), and the pituitary (25%).[1] Other organs involved are the liver, spleen, the hematopoietic system and the lungs (15% each), lymph nodes (5–10%), and the central nervous system other than the pituitary (2–4%). The clinical course may vary from a self-limiting single-system disease to a rapidly progressive multisystem one that, might lead to death. Between 30% and 40% of patients may develop permanent disease-related sequelae. Treatment options vary depending on extent and disease severity at onset. Response to front-line treatment is used to adapt the therapeutic strategy. As LCH is a rare disease, only a limited number of randomized prospective clinical trials are available and some aspects of the patient management remain controversial. Particularly challenging remain patients with multisystem LCH not responding to conventional first-line therapy, those with destructive pulmonary LCH, and those with LCH of the central nervous system of neurodegenerative type (ND-CNS-LCH), and patients with multiple low-risk (e.g. skeletal) relapses.

The presented guidelines are based on published evidence and the collective experience of an expert group. They provide guidance with respect to diagnosis and clinical work-up of LCH manifesting in pediatric and adolescent age. Further, they provide recommendations for front-line treatment based on evidence derived from the prospective clinical trials of the Histiocyte Society and some national groups.[2-9] Second-line and salvage treatment options are less well established in LCH, and therefore, in this regard the current guidelines provide general guidance and expert opinion only. The recommendations can neither replace the physician's own professional judgement nor consider all special clinical circumstances, which may apply to individual cases.

2. PATIENT GROUP

This document refers to Langerhans cell histiocytosis with onset in childhood and adolescence (age < 18 years).

2.1 Diagnostic Criteria

Since LCH may affect any organ or system of the body, the disease requires high index of suspicion whenever suggestive clinical manifestations or imaging findings occur. Table I shows a list of common differential diagnoses depending on presenting complaints, signs, or symptoms.

Table I. Common differential diagnoses of LCH

Affected organ	Manifestation /finding	Differentials
Skin	Vesicles and bullae (most common in early infancy)	Erythema toxicum Herpes simplex Varicella
	Dermatitis (most frequently scalp, diaper area, or axilla) Nodules ("blueberry muffin" like) Petechia Pruritus	Seborrheic dermatitis Mastocytosis Juvenile xanthogranuloma Neuroblastoma Infant leukemia Intrauterine infections Scabies
Bone	Vertebral lesions (vertebra plana)	Ewing sarcoma Septic osteomyelitis Chronic relapsing multifocal osteomyelitis (CRMO) Leukemia / Lymphoma Aneurysmal bone cyst Erdheim-Chester disease Metabolic bone diseases
	Temporal bone	Chronic otitis media Mastoiditis Cholesteatoma Soft tissue sarcoma
	Orbit	Acute infection (preseptal cellulitis) Dermoid cyst Erdheim–Chester disease Pseudoinflammatory tumor Rhabdomyosarcoma Neuroblastoma
	Lytic lesions of the long bones	Septic osteomyelitis CRMO Aneurysmal bone cyst Bone angiomatosis (Gorham disease) Fibrous dysplasia Giant cell tumor of bone Atypical mycobacterial infection Osteogenic sarcoma Ewing's sarcoma
Lung	Respiratory symptoms, reticular lesions (nodules and cysts)	Mycobacterial or other pulmonary infections Sarcoidosis
Liver	Hepatomegaly, jaundice with direct hyperbilirubinemia Hypoalbuminemia	Chronic destructive cholangitis Metabolic diseases Hepatitis Diseases obstructing biliary tract

		Inherited diseases of bilirubin conjugation Toxic (Reye syndrome) Neonatal hemochromatosis Chronic inflammatory bowel disease
Endocrine glands (pituitary, thyroid)	Polyuria/polydipsia, growth failure, hypothyroidism, hypogonadism	Renal diabetes insipidus Head trauma Germ cell tumors of CNS Lymphatic hypophysitis Non-LCH histiocytoses

2.1.1 Histopathology

Due to the extremely heterogeneous clinical spectrum of LCH and the non-pathognomonic imaging findings, tissue examination is mandatory for confirmation of the diagnosis. To avoid pitfalls (e.g. reactive changes in skin or regional lymph nodes), however, pathology findings require interpretation in view of the clinical setting.

2.1.1.1

The diagnosis of LCH is based on histological and immunohistochemical 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 mandatory for definitive diagnosis. [10-12] Since it has been demonstrated that the expression of Langerin confirms the presence of Birbeck granules,[13] the previous diagnostic “gold standard”, namely ultrastructural demonstration of cytoplasmic Birbeck granules by electron microscopy, is no longer required.

2.1.1.2

In the case of isolated vertebra plana without a soft tissue component the risk of biopsy may outweigh the need for a tissue diagnosis. In this case, biopsy could be waived, but the patient should be closely followed to exclude malignancy. The issue of risky biopsy applies also to cases of isolated pituitary/hypothalamic lesion.[14]

2.1.2 Molecular pathology

The 2010 landmark paper by Badalian-Very et al describing the presence of BRAF-V600E mutation in CD1a+ histiocytes and some subsequent publications have redefined LCH as a myeloid neoplasia.[15, 16] Genetic profiling has uncovered several additional genomic MAPK alterations in LCH, all of which uniformly result in constitutive ERK activation.[17-21] Recent publications suggest that the BRAFV600E mutation is associated with more severe disease phenotype and an increased risk for relapsing

course in patients with multisystem LCH.[22-25] Identifying the underlying mutation in each case has an implication for monitoring disease activity /treatment response and well as for targeted salvage therapy in patients who fail standard treatment. Therefore, molecular pathology is required at least if patients with multisystem LCH. In the largest series published to date 50-60% of the patients carry the BRAFV600E mutation and another 15-20% have less common mutations in genes coding proteins of the MAPK pathway.[18] Appropriate sequencing panel should cover BRAF, ARAF, MAP2K1 and MAP3K1 genes.

2.2 Imaging

Although skeletal lesions are characteristic and often give clue toward LCH, imaging findings are not pathognomonic and are therefore not reliable for diagnostic confirmation.

2.2.1 Radiography

At present, the skeletal survey (whole-body X-ray examination) is considered “the gold standard” for detection of skeletal lesions among LCH experts.[1] Major disadvantages of the radiography are the radiation load, the low sensitivity for early lesions and for certain locations (e.g. skull base and vertebral column).

The LCH osseous lesions present on conventional radiography as "punched-out" osteolytic areas. In the long bones, periosteal reaction can be present. The lesion characteristics change depending on the healing phase, so that the process of healing in the X-ray image is visible.

The superiority of conventional radiography in the detection of LCH lesions compared to Technetium^{99} (Te^{99}) scan is well documented.

2.2.2 Computed tomography (CT)

Bone lesions are well seen on CT. Therefore, CT is a useful investigation to delineate uncertain lesions on radiographs. Contrast images delineate the soft tissue involvement and periosteal reaction. The main disadvantage of CT is its considerable radiation load and its inferiority to MRI for the imaging of brain and soft tissue masses.

2.2.3 MRI

The advantage of MRI is the detection of both osseous and extra-osseous lesions without radiation exposure. Due to the encouraging experience in pediatric solid tumors,[26-29] whole body MRI (WB-MRI) is increasingly used for initial and follow-up evaluation of the extent of disease in LCH patients. While the superiority of MRI compared to conventional radiography is undisputable, the excellent prognosis of non-systemically treated patients with unifocal skeletal LCH (as detected by skeletal survey) should be kept in mind.[30] The higher sensitivity of WB-MRI may result in staging upgrade, and thus in unnecessary overtreatment of patients compared to historical controls.

2.2.4 Functional imaging

Technetium[99] scans are less sensitive than radiography, particularly in the assessment of the spine and the pelvic bones. Therefore, technetium scan is considered as a complementary technique only.

FDG-PET is a sensitive technique for identifying active lesions. PET scans have the advantage to differentiate active from non-active bone lesions, and seems to be the optimal technique for assessing treatment response of skeletal lesions. It demonstrates normalization of uptake in a treated lesion earlier than bone scan and radiography.[31] PET, particularly used concomitantly with fusion of CT and MRI, may be a useful modality to evaluate therapy, but radiation burden, need for sedation, cost, and availability limit its usefulness.

2.3 Diagnostic evaluation and clinical classification pre-treatment and at relapse

After confirmation of the diagnosis, it is important to collect further baseline information in order to decide on a therapeutic approach.

2.3.1 Medical history

A complete history should include special reference to: duration of symptoms, pain, swelling, skin rashes, ear discharge, irritability, fever, loss of appetite, weight loss or poor weight gain, growth failure, polydipsia, polyuria, diarrhea, changes in activity level, dyspnea, cigarette smoke exposure, behavioral and neurological changes.

2.3.2 Physical examination

The 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, liver and spleen size, presence of neurological signs and/or symptoms.

2.3.3 Laboratory tests and imaging

2.3.3.1 Mandatory baseline evaluation

The investigations listed in Table I are mandatory for all patients at initial presentation, as well as at disease progression or relapse.

Table I: Mandatory baseline evaluation upon initial diagnosis, progression or relapse

Complete blood counts:

- Hemoglobin, white blood cell and differential count, platelet count
- ESR

Blood chemistry:

- Total protein, albumin, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, γGT
- BUN, creatinine, electrolytes
- Ferritin

Coagulation studies:

- PT, APTT/PTT, fibrinogen

Early morning urine sample:

- Specific gravity and osmolality (morning urine sample)

Abdominal ultrasound:

- Size and structure of liver and spleen

Chest radiograph (CXR)

Skeletal radiograph survey*

* Only bone lesions confirmed by x-ray, CT, functional imaging (bone scan or PET), and/or pathology count for stratification. Marrow signal alterations detected by MRI need confirmation by x-ray, CT, functional imaging or pathology.

2.3.3.2 Investigations upon specific indications

Specific indications may require additional tests. Those are summarized in Table III.

Table III: Laboratory investigations and imaging recommended upon specific indications

Indication	Assessment test
Risk organ involvement	• HLA tissue typing
Bi- or pancytopenia, or persistent unexplained single cytopenia	• Bone marrow aspirate & trephine biopsy to also 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)	• Low dose multi-detector volume-CT if available is preferable to high resolution computed tomography (HR-CT) of the lungs • Lung function test (if age appropriate)
Abnormal lung CT AND findings not characteristic for LCH or suspicion for atypical infection*	• Bronchoalveolar lavage (BAL), >5% CD1a-positive cells in BAL fluid is diagnostic in non-smokers • Lung biopsy (if BAL not diagnostic)
Suspected craniofacial bone lesions including maxilla (mandible excluded)	• MRI of head** • CT could be considered in addition, if needed for better view of skeletal lesions
Suspected vertebral lesions	• MRI of spine (to exclude spinal cord compression and evaluate soft tissue masses)
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) **and/or Imaging abnormality of hypothalamus/ pituitary**	• Endocrine assessment (including water deprivation test and dynamic tests of the anterior pituitary) • MRI of head**
Aural discharge or suspected hearing impairment/mastoid involvement	• Formal hearing assessment • MRI of head** • CT of temporal bone
Unexplained chronic diarrhea, failure to thrive or evidence of malabsorption	• Endoscopy and biopsy

* In case of verified LCH in other organs, biopsy is indicated **ONLY** if the pulmonary findings on CT are inconsistent with LCH or atypical infection is suspected

MRI of the brain to be performed according to the uniform requirements specified in **Appendix 2

2.3.4 Definition of organ involvement

2.3.4.1 Risk organs

Risk organs are organs conferring risk for disease-related mortality. Involvement of the hematopoietic system, the liver or the spleen are considered risk organ involvement. [32, 33] The lung was previously also considered a risk organ but more recently, analysis of a large cohort questioned the independent prognostic value of lung involvement.[34] Due to the frequent association of pulmonary involvement with involvement of other risk organs, the low relative hazard ratio in a multivariate analysis, and finally yet importantly, the very difficult and subjective assessment of disease activity and therapy response in this organ, lungs is no longer counted to the risk organs. For current definition of risk organs see **Appendix 1**.

2.3.4.2 Non-risk organs

Lung involvement

Lung involvement in patients with verified LCH is defined by computer tomography (HR-CT or in small children preferably low dose multi-detector volume-CT)[35]. In a case of verified LCH in other organs, biopsy is indicated only if the pulmonary CT findings are considered atypical or inconsistent with LCH.

Histopathological confirmation is obligatory in patients with isolated pulmonary LCH.

Skeletal involvement

Involvement of two or more anatomically separate bones is categorized as “multifocal bone disease”. Involvement of a single bone is categorized as “single site bone disease” independent of the number of lesions. A retrospective data analysis of a large international cohort suggested that involvement of the craniofacial bones (i.e. orbit, temporal bone, mastoid, sphenoid, zygomatic, ethmoid, maxilla, paranasal sinuses, or cranial fossa) with or without intracranial soft tissue extension, is associated with increased risk for neurological and endocrine sequelae, and thus the term “CNS-risk lesions” was coined for lesions in those bones.[36, 37]

Brain involvement

Granulomatous (tumorous) lesions of the CNS are defined as space-occupying lesions involving brain structures. Any of the following brain regions may be involved either by isolated lesions or in the context of multisystem disease: hypothalamic-pituitary region (HPR), pineal gland, meninges or choroid plexus.[36]

This definition does not include dural enhancement caused by a skull lesion, as often seen in skull vault lesions.

Non-granulomatous (neurodegenerative) lesions encompass **two subtypes**:

- **Radiological neurodegeneration** refers to typical signal changes [38] on 2 consecutive MRI scans performed within an interval of at least 3 months without related clinical manifestations.
- **Clinical neurodegeneration** is defined as the presence of manifest neurological or neuropsychological deficits in the context of consistent radiological findings. [38]

2.3.5 Clinical classification

The clinical classification of LCH is provided in **Appendix 1.**

2.3.6 Treatment stratification

Patients with single skeletal lesions other than "CNS-risk lesions" usually do not need systemic treatment (except for large symptomatic lesions or lesions in weight-bearing bones, which are not easily accessible for surgical treatment). Treatment of isolated cutaneous LCH is controversial, but if topical treatments fail, systemic treatment should be considered in infants.

Multisystem LCH and multifocal skeletal disease indicate systemic treatment.

3. TREATMENT DETAILS

The experience from institutional cohorts, registries and clinical trials has unequivocally proven that treatment of LCH has to be tailored to disease extent and severity and to take into account mortality risk. For this purpose, standardized clinical evaluation of each patient at initial diagnosis and relapse is mandatory.[1, 39, 40]

3.1 Treatment

3.1.1 Treatment of localized LCH

Randomized prospective trials for the treatment of localized LCH are not available. Therefore, current treatment recommendations for localized LCH based on experience gained from retrospective cohorts.[7, 30, 41-46] According to existing clinical experience, the majority of patients with localized LCH (mostly confined to skeleton) do not need systemic treatment. Established treatment options range from expectant attitude,

through surgery or topical drug application, to systemic therapy in selected cases. Decisive for the treatment decision in unifocal skeletal LCH is the location (weight-bearing bones or imminent compression of adjacent structures), the size, the surgical accessibility, the presence of considerable adjacent soft-tissue mass, pain or functional impairment, and the risk of permanent consequences.[47]

3.1.1.1 Wait and see

A “wait and see” approach is justified in small asymptomatic osseous or cutaneous lesions in view of the high likelihood for spontaneous healing.

3.1.1.2 Surgery

Surgical procedures such as biopsy, curettage, or resection are used to treat solitary bone lesions, solitary affected lymph nodes, or solitary circumscribed nodular skin lesions. A biopsy is necessary to confirm the diagnosis and at the same time represents a healing stimulus. Clinical experience showed that radical surgery is not necessary and usually not useful in localized LCH.[1, 39] Wide surgical resection is particularly harmful in skull vault and jawbone lesions, as it impedes bone remodelling and causes permanent defects, which are less often observed in non-resected lesions.

3.1.1.3 Topical steroids

An intralesional application of crystalline methylprednisolone (100-150mg) in symptomatic bone lesion can quickly bring about a reduction in symptoms and facilitated cure.[48, 49]

3.1.1.4 Radiation therapy

Because of its potential to induce secondary malignancies, radiotherapy at a low dose (6-10 Gy) is limited to specific indications (for example, imminent compression of vital structures (e.g. the spinal cord or the optic nerve). It is generally avoided.

3.1.1.5 Systemic therapy

In case of large, symptomatic lesions, which are not easily accessible and bear high likelihood for pathologic fractures and permanent consequences, mild systemic treatment of short duration (3-6 months) using the same regimens as in disseminated LCH, may be the preferable option for local disease control. A best practice based treatment approach to SS-LCH is depicted on **Figure 1**.

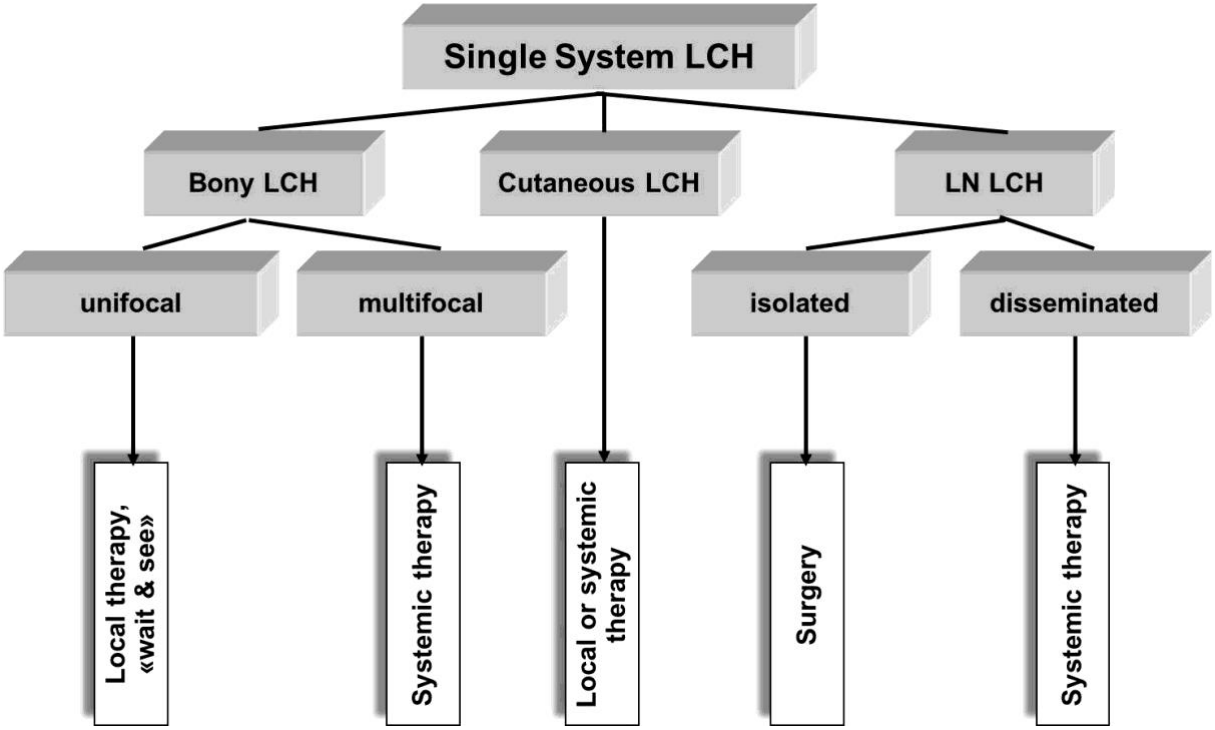

Figure 1. Treatment approach to single-system LCH

3.1.2 Treatment of multifocal skeletal and multisystem LCH

Multifocal skeletal and multisystem LCH (earlier unified under the term disseminated LCH) have been traditionally considered an indication for systemic treatment. While there is a general agreement on the indication of systemic therapy for patients with MS-LCH[50-54], the value of systemic therapy for multifocal skeletal SS-LCH is less well documented and still needs evaluation in controlled prospective trials.

Most trials before the era of international cooperation under the umbrella of the Histiocyte Society have pooled patients with varying clinical presentation, course, and prognosis in order to collect higher numbers.[55]

Regarding individual drugs, drug combinations and regimens with established activity in disseminated LCH we refer to respective extensive reviews.[39, 50, 53, 54, 56] The following review focuses on the results of the clinical trials of the Histiocyte Society [3-5, 57-59]. Finally, we will provide the current standard of care, based on the evidence those trials have provided.

The LCH-I trial (1991-1995) was the first international randomized trial for MS-LCH. It compared the effectiveness of vinblastine and etoposide in the treatment of patients with MS-LCH and the main conclusion was that these drugs are equivalent single-

agent treatments for children with MS-LCH.[3] In addition this trial has proven that based on age and organ involvement at diagnosis, it is possible to define a subgroup of MS-LCH with survival probability of 100% (low risk group) and a subgroup at risk for mortality (risk group).[3]

The LCH-II trial (1996-2000) explored the value of the addition of etoposide to a standard initial therapy combination of prednisolone and vinblastine in patients with risk MS-LCH.[4] The continuation therapy included oral mercaptopurine and pulses of prednisolone and vinblastine for total treatment duration of 6 months. The outcomes in the standard and the experimental arm were similar with respect to response at week 6 (63% vs. 71%), 5-years survival (74% vs. 79%), reactivation frequency (46% vs. 46%), and permanent consequences (43% vs. 37%). This trial proved that the stratification in low risk and risk group based solely on organ involvement at time of diagnosis (age did not prove to have an independent prognostic value) is feasible.

In the LCH-III (2001-2008) trial patients with MS-LCH were divided into two groups (low-risk and risk) depending on risk for mortality. In the low-risk group, the value of the continuation therapy (6 months vs. 12 months) was studied with respect to reactivation rate and sequelae. In the risk group, the value of the addition of intermediate-dose methotrexate to the standard combination of prednisolone and vinblastine was studied with respect to early response and mortality. A second 6-week course of initial therapy was delivered in patients without optimal response in both groups. The results of the risk group trial did not prove superiority of the experimental arm (addition of methotrexate) with respect to initial response, overall and reactivation-free survival and toxicity.[5] In the low-risk group, prolongation of the treatment duration resulted in reduced risk for reactivation (0.50 in the 6-month vs. 0.35 in the 12-month arm).[5] Overall, the LCH-III study concluded that early intensification with a second induction phase for patients with slow responses, and therapy prolongation result in significantly improved outcomes for patients with MS-LCH.

The cumulative experience of the prospective clinical trials conducted by the Histiocyte Society can be summarized as follows:

- Risk organ involvement at diagnosis (defined as at least one of the following: peripheral blood cytopenia and/or liver enlargement ± organ dysfunction and/or spleen enlargement) allows stratification of MS-LCH into low risk (probability of

survival of nearly 100%) and risk group (probability of survival of 80-90%). Patients with risk organ involvement (particularly those with bi-, pancytopenia and liver dysfunction), who do not respond to 6 weeks of standard treatment have particularly dismal prognosis (survival less than 50%). This small subgroup categorized as “very high risk” deserves treatment intensification. As continuing standard treatment usually fails to change the outcome for those patients, experimental approaches targeting improved survival seem justified. To date only few options have shown promising results in the treatment of severe progressive LCH in small series and pilot trials.[57, 60-62] Their applicability is limited by either high toxicity or availability of matched donors, as well as by the need of highly specialized expertise for treatment delivery.

- The standard front-line therapy for patients with MS-LCH treated outside of controlled clinical trials should consist of a 6-12 weeks of initial therapy (oral steroids and weekly vinblastine injections), followed by pulses of prednisolone/vinblastine every 3 weeks, for a total treatment duration of 12 months.
- A standard of care for patients who fail front-line therapy (suboptimal response, disease progression or relapse) but the disease is not life-threatening (low risk LCH), remains to be established. Controlled prospective trials with appropriate endpoints (prevention of subsequent relapses and permanent consequences, as well as, improvement of quality of life) are still lacking.
- The same is true for some specific or rare clinical scenarios, i.e. isolated destructive pulmonary LCH, sclerosing cholangitis, LCH reactivation presenting with isolated diabetes insipidus, CNS-LCH of neurodegenerative type.

A currently ongoing international trial of the Histiocyte Society (LCH-IV International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis; NCT02205762) with a complex design (5 interventional and 2 observational strata) is looking for improvement of relapse-free survival and quality of life by targeting still unsolved clinical issues.[55, 56]

3.1.2.1 Front-line treatment

The combination of prednisolone plus vinblastine is the most extensively studied first-line therapy in pediatric-onset LCH.[4, 5, 9, 63-65] The major advantages are its extensively documented activity, its favorable toxicity profile and good tolerability in children, and

its moderate costs, which make this treatment applicable even in countries with limited health-care resources.[55] In 'high-risk' patients of the LCH-III trial, the prednisolone plus vinblastine combination has induced response in risk organs in 70% of the patients after 6–12 weeks of treatment, and resulted in an overall 5-year survival of 84%, and a reactivation-free survival of 73%.[5]

This regimen is the current standard frontline therapy for pediatric patients with multifocal and multisystem LCH treated outside of clinical trials (**Figures 2 and 3**). It consists of 6–12 weeks of initial therapy (oral steroids and weekly vinblastine injections), followed by a continuation therapy given to total treatment duration of 12 months. The continuation therapy consists of prednisolone (day 1–5)/ vinblastine (day 1) pulses given every 3 weeks.

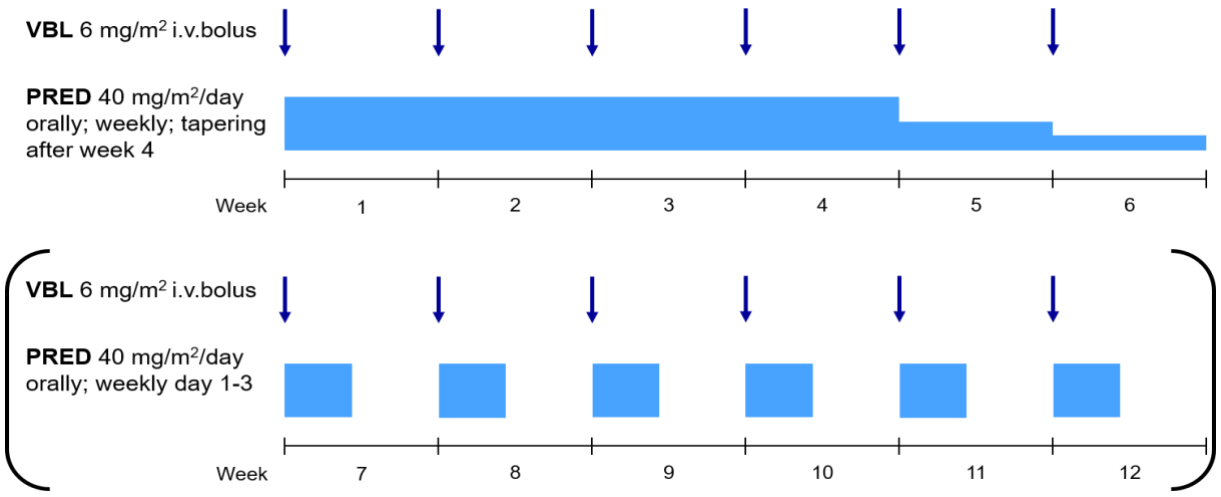

Figure 2. Initial treatment for multisystem LCH

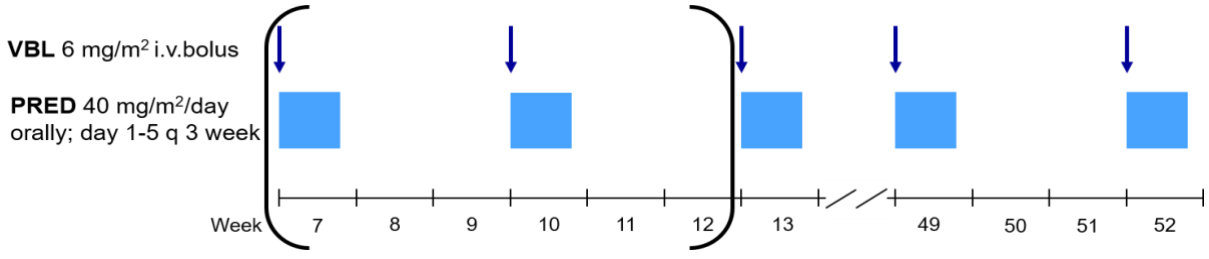

Figure 3. Continuation treatment for multisystem LCH

3.1.2.2 Second-line treatment options for non-risk LCH relapses

There are still no published prospective trials on treatment of LCH relapses. Relapses of LCH, however, are associated with an increased risk of permanent consequences.[66-68] The belief that control of the disease will prevent subsequent relapses and, thus,

related permanent consequences, prompts physicians to use systemic chemotherapy for 'low-risk' multisystem LCH.

Patients with low-risk disease, particularly those, who have a relapse after complete resolution, can be cured by repetition of the front-line regimen, or by application of a number of other single drugs or drug combinations.[50, 54, 56, 59, 66-68] Therefore, second-line treatment of non-risk LCH and beyond should be offered preferably within controlled trials. Future trials seeking effective treatment for 'low-risk' LCH should focus on appropriate end-points such as quality of life, risk for and severity of permanent consequences, instead on control of active lesions.[69] Such trials are only possible within the frame of a large-scale cooperation and require implementation of innovative study designs and appropriate statistical methods.

For treatment outside of clinical trials, the following regimens seem to be reasonable choices, based existing evidence for activity in LCH or experience from the clinical practice, as well as, justifiable toxicity:

- Patients who recur months or years after stopping prednisone and vinblastine can benefit from re-induction of the first-line regimen.[30]
- An alternative treatment regimen employs vincristine, prednisone, and cytosine arabinoside.[70] This regimen, modified for prednisolone duration, is being prospectively tested in the LCH-IV trial.
- Cytosine-arabinoside has been used with success in patients with extracranial non-risk LCH and in CNS-LCH.[39, 71]
- 2-Cholorodeoxyadenosine (2-CdA, Cladribine®, Leustatin®) at 5 mg/m2/day for 5 days per course has also been shown to be effective therapy for recurrent low-risk LCH (multifocal bone and low-risk multisystem LCH) with acceptable toxicity.[59] Use of 2-CdA should be limited to a maximum of six cycles to avoid cumulative toxicity and potentially long-lasting or irreversible cytopenias.
- Clofarabine is a proven effective therapy for patients with multiple relapses of low-risk or high-risk organs.[39, 72-74] In LCH it is usually applied at a dose of 25mg/m^2/day for 5 days every 28 days for six cycles. Depending on hematopoietic toxicity or the need for longer treatment, (further) cycles at the same daily dose, but reduced to 3 days can be given.
- Bisphosphonate therapy has reported effects in treating recurrent skeletal LCH.[75-78] The regimen most commonly used in children consist of six doses of

pamidronate at 1 mg/kg, given at 4-week intervals. Other bisphosphonates, such as zoledronate and oral alendronate, have also been successful in treating bone LCH.

The choice of an individual drug or regimen requires consideration of preceding treatments, cumulative toxicities and known individual intolerances and side effects. The decision remains on discretion of the treating physician, as the level of published evidence is not sufficient for a clear recommendation of a particular regimen or for a ranked recommendation.

Effective treatments are still not available for the most severe disease-related sequelae (such as neurodegeneration, sclerosing cholangitis, and lung honeycombing).

3.1.2.3 Salvage treatment options for severe progressing multisystem LCH (very high risk LCH).

The curative potential of the combination of 2-CdA and Ara-C in patients with severe refractory to front-line systemic therapy multisystem LCH has been confirmed by two prospective trials.[57, 60] Unfortunately, this regimen is highly myelotoxic and associated with treatment-related mortality even if applied with experienced centers.[57] Allogeneic hematopoietic stem cell transplantation is another treatment option for very high-risk multisystem LCH with curative rate comparable to those achieved with 2-CdA and Ara-C.[61, 79] However, the most optimal conditioning regimen remains to be defined.[79]

3.1.2.4 Approaching molecular targets.

The mitogen-activated protein kinase (MAPK) signalling pathway plays a key role in the regulation of gene expression, cellular growth and survival. A number of activating mutations affecting this pathway result in overactive downstream extracellular-signal-regulated kinase (ERK), which proves to be the ultimate driving event in LCH. Both specific inhibition of the mutated kinases, as well as, downstream ERK inhibition (**Figure 4**) are undoubtedly appealing treatment options. [17, 39, 80, 81]

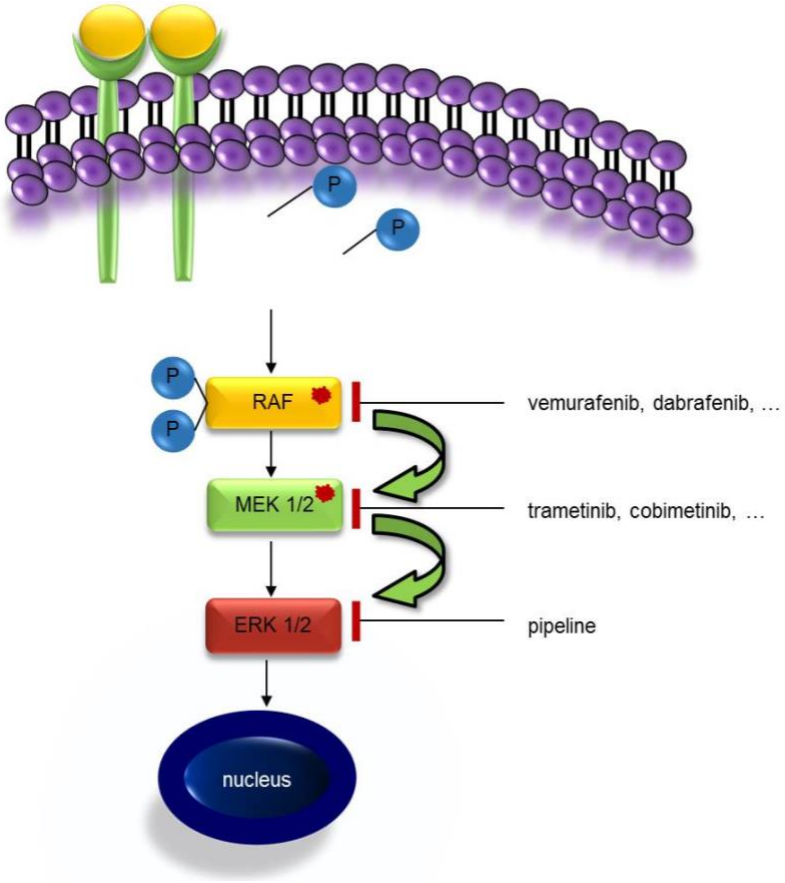

Figure 4. Options for targeted LCH treatment

The clinical experience available to date confirmed at least two essential expectations to BRAF inhibitors, namely in vivo activity in patients with LCH and ECD and rapid clinical response.[82-86] In patients with severe life-threatening LCH rapid clinical response is of particular importance. Currently published pediatric series show impressive rapid response to vemurafenib and prove that sustainable treatment effect can be achieved with BRAF inhibitors.[25, 87] However, most patients experience disease relapse shortly after treatment discontinuation. Hence, it is currently unclear whether treatment with a single inhibitor can eradicate the disease. The major tasks to be addressed in controlled prospective trials are therefore: finding the most effective and least toxic specific inhibitors, establishing downstream inhibition for patients without known mutations, defining appropriate pediatric dosages, and establishing how long and in which combinations (if any) the drugs should be given.

3.2 Assessments

Besides baseline evaluation at initial diagnosis and at relapse (described in Section 2.3), assessment of disease activity, and respectively of response to treatment, are recommended upon completion of initial (week 7 or 13) and of continuation therapy.

The recommended assessment tests and time points are presented in **Appendix 3**

3.2.1 Response categories of the LCH Working Group of the Histiocyte Society

There are three categories of response: *Better, Intermediate and Worse*. They express a comparison of a current disease state to that at the last previous assessment.

Table II: Definition of response categories

Response category	Definition
BETTER	• Complete disease resolution (NAD) • Regression (AD better)
INTERMEDIATE	• Stable (unchanged)
WORSE	• Progression*

***** Progression of skeletal lesions is defined as unequivocal enlargement of the size of existing lesions and/or appearance of new lesions; in patients with risk organ involvement the overall response (and hence the therapeutic decision) depends on response in risk organs.
Those categories do not apply for evaluation of severity and response in neurodegenerative CNS LCH (ND-CNS-LCH).

3.2.2 Disease activity score

The Disease Activity Score (DAS) developed by the French LCH Study Group allows for a more exact and objective assessment of the patient's general condition and of therapy response in cases with very severe disease.

Table III: Disease Activity Score [88]

Variable	Modality	Score
Bone (a)	Pain No pain	1 0
Bone (b)	Compressing other organs (orbit or spine) No compression	2 0
Fever (>38.5 °C)	Yes No	1 0
Lung: imaging	Pneumothorax Interstitial lesion on chest x-ray film or lung CT scan Normal chest x-ray film or lung CT scan	2 1 0
Lung: function	Mechanical ventilation or PFT <50% Supplemental oxygen or PFT between 50-80% No dysfunction, no cyanosis, no supplemental oxygen	5 2 0

Skin: area involved	25% 5-25% Below 5%	2 1 0
Soft tissue tumor (including CNS)	5 cm max diameter 2-5 cm max diameter 0-2 cm max diameter	2 1 0
Nodes (> 2 cm)	Yes No	1 0
Liver	Below umbilicus Enlarged above umbilicus Not enlarged	2 1 0
Spleen	Below umbilicus Enlarged above umbilicus Not enlarged	2 1 0
Liver (enzymes)	>10 N 3 - 10 N < 3 N	2 1 0
Liver (gamma GT)	> 10 N 3 - 10 N < 3 N	2 1 0
Albumin	Perfusion required in past week No perfusion, but < 30 g/L > 30 g/L	3 1 0
Platelet: requirements in past week	More than 2 transfusions 1 or 2 transfusions Low platelet count (PLT < 100 x10^9/L), no transfusion Normal count	4 3 2 0
Red cells: requirements in past week	more than 2 units (> 20 ml/kg/week) 1 or 2 units (10-20 ml/kg/week) Hb below 100 g/L, no transfusion No transfusion	4 3 1 0

There is a correlation between the two response assessment tools (**Table VI**).

Table IV: Response assessment in LCH

Response category (HS criteria)		**Disease severity score**
Response	Non-Active Disease	Absolute Score 0-1
	AD better	Absolute Score 2-7 AND decrease of ≥4 points compared to pre-salvage evaluation
Non-response	AD intermediate	Absolute Score 2-7 AND decrease of <4 points or Absolute Score >7 AND no increase of score compared to pre-salvage evaluation
	AD worse	Any increase of score compared to pre-salvage evaluation

3.3 Summary of known adverse events associated with treatment recommendation

3.3.1 Steroids (Prednisone, Prednisolone)

- Arterial hypertension
- Hyperglycemia
- Pancreatitis
- Increased susceptibility to infections
- Mood changes and psychotic reactions

3.3.2 Vinblastine

- Hematologic toxicity
- Neuropathic pain
- Vocal cord paralysis
- Foot drop, paresis
- Jaw pain
- Constipation or ileus

3.3.3 6-mercaptopurine

- Hematologic toxicity
- Hepatic toxicity

3.4 Dose Modifications and delays

3.4.1 Dose modifications for age and body weight

For children weighing less than 10 Kg:
Prednisone (PRED): 1.3 mg/kg/day in three divided doses
Vinblastine (VBL): 0.2 mg/kg/dose
6-mercaptopurine (6-MP): 1.7 mg/kg/day in a single dose

3.4.2 Dose modifications for toxicity

3.4.2.1 Steroids

- Hypertension:

Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

- Hyperglycemia:

Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

- Pancreatitis:

Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic

pancreatitis or severe pancreatitis (abdominal pain >72 hours and ≥ Grade 3 amylase elevation (≥ 2.0x ULN).

- Varicella:

Steroids should be held during active infection. Do not hold during incubation period following exposure.

- Inability to use oral doses:

Substitute IV methyl-prednisolone at 80% of the oral prednisone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same; prednisone is converted in the liver to prednisolone.

- Severe infection:

Do not hold or discontinue steroids during induction without serious consideration.

- Severe psychosis:

Steroid dose may be reduced by 50%.

3.4.2.2 Vinblastine

Modified “Balis” scale recommended for grading peripheral neuropathy in children.

- Severe neuropathic pain (Grade 3 or greater):

Hold dose(s). When symptoms subside, resume at 50% previous dose, then escalate to full dose as tolerated.

- Vocal Cord paralysis:

Hold dose(s). When symptoms subside, resume at 50% previous dose, then escalate to full dose as tolerated.

- Foot Drop, paresis:

Should be Grade 3 to consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vinblastine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure.

- Jaw pain:

Treat with analgesics; do not modify vinblastine dose.

- Hyperbilirubinemia

Direct Bilirubin		Dose reduction of vinblastine
[µmol/L]	[mg/dl]	

< 53.0	< 3.1	FULL dose
53.0-85.5	3.1-5.0	reduce by 50%
85.6-103.0	5.1-6.0	reduce by 75%
>103	> 6.0	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

- Constipation or ileus (≥ Grade 3) or typhlitis:

Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% dose and escalate to full dose as tolerated.

3.4.2.3 6-mercaptopurine (6-MP)

- Hematologic toxicity:

If absolute neutrophil count (ANC) falls below 0.5 x109/L (500/µL) or if platelet count falls below 50 x109/L (50,000/µL), hold 6-MP until recovery above these levels.

For the first drop in ANC or platelets, resume chemotherapy at 100% after ANC is ≥ 0.75 x109/L (750/µL) and platelets ≥ 75 x109/L (75,000/µL).

If ANC falls below 0.5 x109/L (500/µL), or if platelet count falls below 50 x109/L (50,000/µL) for a second time, discontinue doses until ANC is ≥ 0.75 x109/L (750/µL) and platelets are ≥ 75 x109/L (75,000/µL). Restart 6-MP at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-4 week intervals provided ANC remains ≥ 0.75 x109/L (750/µL) and platelets remain ≥ 75 x109/L (75,000/µL).

If ANC falls below 0.5 x109/L (500/µL) or if platelet count falls below 50 x109/L (50,000/µL) on ≥ 2 occasions, consider thiopurine pharmacology testing. Should therapy be withheld for myelosuppression or elevated transaminases, do not “make up” that week. Resume therapy at the correct point, chronologically.

- Hepatic toxicity:

For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total bilirubin. Monitor SGPT/ALT or SGOT/AST and total bilirubin every 4 weeks as long as transaminases remain over 5x ULN. Continue full dose therapy unless either of the following occurs:

1) Direct bilirubin >34.2 µmol/L (>2.0 mg/dL)

2) SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) on two determinations at least one week apart.

If either of these occurs, hold 6-MP and monitor labs (as above) weekly. Restart therapy at full dose when the transaminase is less than 5x ULN and bilirubin is normal. If liver dysfunction persists, sclerosing cholangitis should be considered and excluded, and alternative therapy should be considered.

3.5 Supportive Treatment

3.5.1 Gastric protection

Gastric protection concomitant to steroids is recommended. H-2 inhibitors (e.g. Ranitidine), proton pump blockers (e.g. Omeprazole), or Sucralfate could be used depending on local preferences.

3.5.2 Pneumocystis jiroveci prophylaxis

Oral sulphamethoxazole/trimethoprim, 5 mg/kg/day of the trimethoprime, divided into 2 doses/day, on 3 days per week (or per local protocol) is recommended throughout the study period and for 12 weeks thereafter.

3.5.3 Antiemetics

Antiemetics to be given as necessary according to local practices.

3.5.4 Transfusions

Blood cell components should be filtered and irradiated (>25 Gy) for prevention of GvHD according to local practice.

3.6 Patient Follow Up

Follow up of the patients serves monitoring remission state and timely recognition of disease- or treatment-related sequelae.

Table VI: Recommended follow-up after end of therapy for pediatric-onset LCH

Indication	Risk for defined sequelae	Investigation/Test	Intervals after end of therapy or disease resolution*
All patients		Ask for polyuria/polydipsia	At each visite
		Clinical examination, height, weight, pubertal status	1st yr: each 3 mo; than each 6 mo until 5 years Thereafter: yearly
Evidence of liver disease (particularly cholestasis) at the end of treatment	Sclerosing cholangitis	GPT, GGT, Bili, ALP Liver sonography	1st yr: each 3 mo; than each 6 mo until 5 yrs Thereafter: yearly
Persisting radiological or clinical pulmonary abnormalities at the end of treatment	Honeycombing, chronic respiratory insufficiency	Pulmonary function tests	1st yr: each 3 mo; than each 6 mo until 5 yrs Thereafter: yearly
		Radiography (or low-dose CT)	1st yr: each 6 mo 2-5 yrs: yearly Thereafter: upon clinical judgment
Previous involvement of the facial bones, jaw, oral mucosa	Abnormal dentition	Dental assessment	As clinically indicated, at least once at 5 years
Previous temporal bone involvement	Hearing loss	Audiology	At school entry and as clinically indicated
History of polyuria/polydipsia	Central diabetes insipidus	Urine osmolality in a morning sample, water deprivation test, MRI	At manifestation
Central diabetes insipidus	Anterior pituitary dysfunction Neurodegeneration	Brain MRI **	1st yr: each 6 mo 2-5 yrs: yearly Thereafter: each 2 yrs
Radiological neurodegeneration	Clinical neurodegeneration	Brain MRI **	1st yr: each 6 mo 2-5 yrs: yearly Thereafter: each 2 yrs
		Neurological exam	1st yr: each 6 mo 2-5 yrs: yearly Thereafter: yearly
		Psychological tests	At end of treatment 2 yearly for 5 years

			Thereafter: upon clinical judgment

* Aftercare recommended for at least 5 years after treatment, preferably until age of 18 (completion of growth and puberty). Beyond 5 years, examinations are recommended yearly or as clinically appropriate in patients with known PC and those being at risk for late manifestations.

** for brain MRI guideline see **Appendix 2**

4. REFERENCE LIST

1. Haupt R, Minkov M, Astigarraga I, Schafer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. Pediatr Blood Cancer. 2013 Feb;60(2):175-84.

2. Ceci A, de Terlizzi M, Colella R, Loiacono G, Balducci D, Surico G, et al. Langerhans cell histiocytosis in childhood: results from the Italian Cooperative AIEOP-CNR-H.X '83 study. Med Pediatr Oncol. 1993;21(4):259-64.

3. 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 May;138(5):728-34.

4. 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 Mar 1;111(5):2556-62.

5. Gadner H, Minkov M, Grois N, Potschger U, Thiem E, Arico M, et al. Therapy prolongation improves outcome in multisystem Langerhans cell histiocytosis. Blood. 2013 Jun 20;121(25):5006-14.

6. Morimoto A, Ikushima S, Kinugawa N, Ishii E, Kohdera U, Sako M, et al. Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis: Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. Cancer. 2006 Aug 1;107(3):613-9.

7. Morimoto A, Ishida Y, Suzuki N, Ohga S, Shioda Y, Okimoto Y, et al. Nationwide survey of single-system single site Langerhans cell histiocytosis in Japan. Pediatr Blood Cancer. 2010 Jan;54(1):98-102.

8. Morimoto A, Shioda Y, Imamura T, Kudo K, Kawaguchi H, Sakashita K, et al. Intensified and prolonged therapy comprising cytarabine, vincristine and prednisolone improves outcome in patients with multisystem Langerhans cell histiocytosis: results of the Japan Langerhans Cell Histiocytosis Study Group-02 Protocol Study. Int J Hematol. 2016 Jul;104(1):99-109.

9. Rigaud C, Barkaoui MA, Thomas C, Bertrand Y, Lambilliotte A, Miron J, et al. Langerhans cell histiocytosis: therapeutic strategy and outcome in a 30-year nationwide cohort of 1478 patients under 18 years of age. Br J Haematol. 2016 Sep;174(6):887-98.

10. 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., eds. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008:358-60.

11. 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 Apr;32(4):615-9.

12. Chikwava K, Jaffe R. Langerin (CD207) staining in normal pediatric tissues, reactive lymph nodes, and childhood histiocytic disorders. Pediatr Dev Pathol. 2004 Nov-Dec;7(6):607-14.

13. 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 Jan;12(1):71-81.

14. Prosch H, Grois N, Prayer D, Waldhauser F, Steiner M, Minkov M, et al. Central diabetes insipidus as presenting symptom of Langerhans cell histiocytosis. Pediatr Blood Cancer. 2004 Oct;43(5):594-9.

15. Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010 Sep 16;116(11):1919-23.

16. Berres ML, Merad M, Allen CE. Progress in understanding the pathogenesis of Langerhans cell histiocytosis: back to Histiocytosis X? Br J Haematol. 2015 Apr;169(1):3-13.

17. Chakraborty R, Hampton OA, Shen X, Simko SJ, Shih A, Abhyankar H, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood. 2014 Nov 6;124(19):3007-15.

18. Durham BH. Molecular characterization of the histiocytoses: Neoplasia of dendritic cells and macrophages. Semin Cell Dev Biol. 2019 Feb;86:62-76.

19. Heritier S, Helias-Rodzewicz Z, Chakraborty R, Sengal AG, Bellanne-Chantelot C, Thomas C, et al. New somatic BRAF splicing mutation in Langerhans cell histiocytosis. Mol Cancer. 2017 Jul 6;16(1):115.

20. Nelson DS, van Halteren A, Quispel WT, van den Bos C, Bovee JV, Patel B, et al. MAP2K1 and MAP3K1 mutations in Langerhans cell histiocytosis. Genes Chromosomes Cancer. 2015 Jun;54(6):361-8.

21. Zarnegar S, Durham BH, Khattar P, Shukla NN, Benayed R, Lacouture ME, et al. Novel activating BRAF fusion identifies a recurrent alternative mechanism for ERK activation in pediatric Langerhans cell histiocytosis. Pediatr Blood Cancer. 2018 Jan;65(1).

22. Heritier S, Helias-Rodzewicz Z, Lapillonne H, Terrones N, Garrigou S, Normand C, et al. Circulating cell-free BRAF(V600E) as a biomarker in children with Langerhans cell histiocytosis. Br J Haematol. 2017 Aug;178(3):457-67.

23. Nann D, Schneckenburger P, Steinhilber J, Metzler G, Beschorner R, Schwarze CP, et al. Pediatric Langerhans cell histiocytosis: the impact of mutational profile on clinical progression and late sequelae. Ann Hematol. 2019 Jul;98(7):1617-26.

24. Heritier S, Emile JF, Barkaoui MA, Thomas C, Fraitag S, Boudjemaa S, et al. BRAF Mutation Correlates With High-Risk Langerhans Cell Histiocytosis and Increased Resistance to First-Line Therapy. J Clin Oncol. 2016 Sep 1;34(25):3023-30.

25. Eckstein OS, Visser J, Rodriguez-Galindo C, Allen CE, Group N-LS. Clinical responses and persistent BRAF V600E(+) blood cells in children with LCH treated with MAPK pathway inhibition. Blood. 2019 Apr 11;133(15):1691-4.

26. Atkin KL, Ditchfield MR. The role of whole-body MRI in pediatric oncology. J Pediatr Hematol Oncol. 2014 Jul;36(5):342-52.

27. Goo HW, Yang DH, Ra YS, Song JS, Im HJ, Seo JJ, et al. Whole-body MRI of Langerhans cell histiocytosis: comparison with radiography and bone scintigraphy. Pediatr Radiol. 2006 Oct;36(10):1019-31.

28. Johnston C, Brennan S, Ford S, Eustace S. Whole body MR imaging: applications in oncology. Eur J Surg Oncol. 2006 Apr;32(3):239-46.

29. Kellenberger CJ, Epelman M, Miller SF, Babyn PS. Fast STIR whole-body MR imaging in children. Radiographics. 2004 Sep-Oct;24(5):1317-30.

30. 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 Aug;37(2):108-14.

31. Binkovitz LA, Olshefski RS, Adler BH. Coincidence FDG-PET in the evaluation of Langerhans' cell histiocytosis: preliminary findings. Pediatr Radiol. 2003 Sep;33(9):598-602.

32. Lahey ME. Prognostic factors in histiocytosis X. Am J Pediatr Hematol Oncol. 1981 Spring;3(1):57-60.

33. 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 Dec;39(6):581-5.

34. Ronceray L, Potschger U, Janka G, Gadner H, Minkov M. Pulmonary involvement in pediatric-onset multisystem langerhans cell histiocytosis: effect on course and outcome. J Pediatr. 2012 Jul;161(1):129-33 e3.

35. Vasallo R, Ryu J, Colby T, Hartman T, Limper A. Pulmonary Langerhans´ cell histiocytosis. N Engl J Med. 2000;342(26):1969-78.

36. Grois N, Fahrner B, Arceci RJ, Henter JI, McClain K, Lassmann H, et al. Central nervous system disease in Langerhans cell histiocytosis. J Pediatr. 2010 Jun;156(6):873-81, 81 e1.

37. 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 Feb;46(2):228-33.

38. Prayer D, Grois N, Prosch H, Gadner H, Barkovich AJ. MR imaging presentation of intracranial disease associated with Langerhans cell histiocytosis. AJNR Am J Neuroradiol. 2004 May;25(5):880-91.

39. Allen CE, Ladisch S, McClain KL. How I treat Langerhans cell histiocytosis. Blood. 2015 Jul 02;126(1):26-35.

40. Broadbent V, Gadner H, Komp DM, Ladisch S. Histiocytosis syndromes in children: II. Approach to the clinical and laboratory evaluation of children with Langerhans cell histiocytosis. Clinical Writing Group of the Histiocyte Society. Med Pediatr Oncol. 1989;17(6):492-5.

41. Berry DH, Gresik M, Maybee D, Marcus R. Histiocytosis X in bone only. Med Pediatr Oncol. 1990;18(4):292-4.

42. Bollini G, Jouve JL, Gentet JC, Jacquemier M, Bouyala JM. Bone lesions in histiocytosis X. J Pediatr Orthop. 1991 Jul-Aug;11(4):469-77.

43. Fiorillo A, Sadile F, De Chiara C, Parasole R, Simeone D, D'Amore R, et al. Bone lesions in Langerhans cell histiocytosis. Clin Pediatr (Phila). 1993 Feb;32(2):118-20.

44. Kilpatrick SE, Wenger DE, Gilchrist GS, Shives TC, Wollan PC, Unni KK. Langerhans' cell histiocytosis (histiocytosis X) of bone. A clinicopathologic analysis of 263 pediatric and adult cases. Cancer. 1995 12/15/1995;76(12):2471-84.

45. Lau LM, Stuurman K, Weitzman S. Skeletal Langerhans cell histiocytosis in children: permanent consequences and health-related quality of life in long-term survivors. Pediatr Blood Cancer. 2008 Mar;50(3):607-12.

46. Womer RB, Raney RB, Jr., D'Angio GJ. Healing rates of treated and untreated bone lesions in histiocytosis X. Pediatrics. 1985 Aug;76(2):286-8.

47. Hutter C, Minkov M. Insights into the pathogenesis of Langerhans cell histiocytosis: the development of targeted therapies. Immunotargets Ther. 2016;5:81-91.

48. Cohen M, Zornoza J, Cangir A, Murray JA, Wallace S. Direct injection of methylprednisolone sodium succinate in the treatment of solitary eosinophilic granuloma of bone: a report of 9 cases. Radiology. 1980 Aug;136(2):289-93.

49. Egeler RM, Thompson RC, Jr., Voute PA, Nesbit ME, Jr. Intralesional infiltration of corticosteroids in localized Langerhans' cell histiocytosis. J Pediatr Orthop. 1992 Nov-Dec;12(6):811-4.

50. Abla O, Egeler RM, Weitzman S. Langerhans cell histiocytosis: Current concepts and treatments. Cancer Treat Rev. 2010 Jun;36(4):354-9.

51. Arceci RJ, Brenner MK, Pritchard J. Controversies and new approaches to treatment of Langerhans cell histiocytosis. Hematol Oncol Clin North Am. 1998 Apr;12(2):339-57.

52. Broadbent V, Gadner H. Current therapy for Langerhans cell histiocytosis. Hematol Oncol Clin North Am. 1998 Apr;12(2):327-38.

53. McClain KL. Drug therapy for the treatment of Langerhans cell histiocytosis. Expert Opin Pharmacother. 2005 Nov;6(14):2435-41.

54. Minkov M. Multisystem Langerhans cell histiocytosis in children: current treatment and future directions. Paediatr Drugs. 2011 Apr 1;13(2):75-86.

55. Minkov M, Rodriguez-Galindo C. Treatment of Langerhans cell histiocytosis: it is time to learn from the past. Br J Haematol. 2015 Oct;171(1):148-9.

56. Monsereenusorn C, Rodriguez-Galindo C. Clinical Characteristics and Treatment of Langerhans Cell Histiocytosis. Hematol Oncol Clin North Am. 2015 Oct;29(5):853-73.

57. Donadieu J, Bernard F, van Noesel M, Barkaoui M, Bardet O, Mura R, et al. Cladribine and cytarabine in refractory multisystem Langerhans cell histiocytosis: results of an international phase 2 study. Blood. 2015 Sep 17;126(12):1415-23.

58. Minkov M, Grois N, Broadbent V, Ceci A, Jakobson A, Ladisch S. Cyclosporine A therapy for multisystem langerhans cell histiocytosis. Med Pediatr Oncol. 1999 Nov;33(5):482-5.

59. Weitzman S, Braier J, Donadieu J, Egeler RM, Grois N, Ladisch S, et al. 2'-Chlorodeoxyadenosine (2-CdA) as salvage therapy for Langerhans cell histiocytosis (LCH). results of the LCH-S-98 protocol of the histiocyte society. Pediatr Blood Cancer. 2009 Dec 15;53(7):1271-6.

60. 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 Nov;41(17):2682-9.

61. 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 Aug;36(3):215-25.

62. Akkari V, Donadieu J, Piguet C, Bordigoni P, Michel G, Blanche S, et al. Hematopoietic stem cell transplantation in patients with severe Langerhans cell histiocytosis and hematological dysfunction: experience of the French Langerhans Cell Study Group. Bone Marrow Transplant. 2003 Jun;31(12):1097-103.

63. Feldges AJ, Imbach P, Pluss HJ, Sartorius J, Wagner HP, Wyss M. [Therapy of juvenile disseminated histiocytosis X. First results of a prospective study at the pediatric section of the Swiss Work Group for Clinical Cancer Research (SAKK)]. Schweiz Med Wochenschr. 1980 Jun 7;110(23):912-5.

64. 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.

65. Lahey ME. Histiocytosis X--comparison of three treatment regimens. J Pediatr. 1975 Aug;87(2):179-83.

66. Minkov M, Steiner M, Potschger U, Arico M, Braier J, Donadieu J, et al. Reactivations in multisystem Langerhans cell histiocytosis: data of the international LCH registry. J Pediatr. 2008 Nov;153(5):700-5, 5 e1-2.

67. Morimoto A, Kobayashi R, Maeda M, Asami K, Bessho F, Imashuku S. Impact of reactivation on the sequelae of multi-system Langerhans cell histiocytosis patients. Pediatr Blood Cancer. 2008 Apr;50(4):931-2; author reply 2.

68. Pollono D, Rey G, Latella A, Rosso D, Chantada G, Braier J. Reactivation and risk of sequelae in Langerhans cell histiocytosis. Pediatr Blood Cancer. 2007 Jun 15;48(7):696-9.

69. Minkov M. Langerhans cell histiocytosis: pragmatic empirism on the road to rational cure. Expert Opin Pharmacother. 2012 Jun 20.

70. 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.

71. Simko SJ, McClain KL, Allen CE. Up-front therapy for LCH: is it time to test an alternative to vinblastine/prednisone? Br J Haematol. 2015 Apr;169(2):299-301.

72. Abraham A, Alsultan A, Jeng M, Rodriguez-Galindo C, Campbell PK. Clofarabine salvage therapy for refractory high-risk langerhans cell histiocytosis. Pediatr Blood Cancer. 2013 Jun;60(6):E19-22.

73. Rodriguez-Galindo C, Jeng M, Khuu P, McCarville MB, Jeha S. Clofarabine in refractory Langerhans cell histiocytosis. Pediatr Blood Cancer. 2008 Nov;51(5):703-6.

74. Simko SJ, Tran HD, Jones J, Bilgi M, Beaupin LK, Coulter D, et al. Clofarabine salvage therapy in refractory multifocal histiocytic disorders, including Langerhans cell histiocytosis, juvenile xanthogranuloma and Rosai-Dorfman disease. Pediatr Blood Cancer. 2014 Mar;61(3):479-87.

75. Arzoo K, Sadeghi S, Pullarkat V. Pamidronate for bone pain from osteolytic lesions in Langerhans'-cell histiocytosis. N Engl J Med. 2001 Jul 19;345(3):225.

76. Brown RE. More on pamidronate in Langerhans'-cell histiocytosis. N Engl J Med. 2001 Nov 15;345(20):1503.

77. Farran RP, Zaretski E, Egeler RM. Treatment of Langerhans cell histiocytosis with pamidronate. J Pediatr Hematol Oncol. 2001 Jan;23(1):54-6.

78. Morimoto A, Shioda Y, Imamura T, Kanegane H, Sato T, Kudo K, et al. Nationwide survey of bisphosphonate therapy for children with reactivated Langerhans cell histiocytosis in Japan. Pediatr Blood Cancer. 2011 Jan;56(1):110-5.

79. Veys PA, Nanduri V, Baker KS, He W, Bandini G, Biondi A, et al. Haematopoietic stem cell transplantation for refractory Langerhans cell histiocytosis: outcome by intensity of conditioning. Br J Haematol. 2015 Jun;169(5):711-8.

80. Rollins BJ. Genomic Alterations in Langerhans Cell Histiocytosis. Hematol Oncol Clin North Am. 2015 Oct;29(5):839-51.

81. Bubolz AM, Weissinger SE, Stenzinger A, Arndt A, Steinestel K, Bruderlein S, et al. Potential clinical implications of BRAF mutations in histiocytic proliferations. Oncotarget. 2014 Jun 30;5(12):4060-70.

82. Charles J, Beani JC, Fiandrino G, Busser B. Major response to vemurafenib in patient with severe cutaneous Langerhans cell histiocytosis harboring BRAF V600E mutation. J Am Acad Dermatol. 2014 Sep;71(3):e97-9.

83. Haroche J, Cohen-Aubart F, Emile JF, Arnaud L, Maksud P, Charlotte F, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood. 2013 Feb 28;121(9):1495-500.

84. Haroche J, Cohen-Aubart F, Emile JF, Maksud P, Drier A, Toledano D, et al. Reproducible and sustained efficacy of targeted therapy with vemurafenib in patients with BRAF(V600E)-mutated Erdheim-Chester disease. J Clin Oncol. 2015 Feb 10;33(5):411-8.

85. Heritier S, Jehanne M, Leverger G, Emile JF, Alvarez JC, Haroche J, et al. Vemurafenib Use in an Infant for High-Risk Langerhans Cell Histiocytosis. JAMA Oncol. 2015 Sep;1(6):836-8.

86. Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. N Engl J Med. 2015 Aug 20;373(8):726-36.

87. Donadieu J, Larabi IA, Tardieu M, Visser J, Hutter C, Sieni E, et al. Vemurafenib for Refractory Multisystem Langerhans Cell Histiocytosis in Children: An International Observational Study. J Clin Oncol. 2019 Nov 1;37(31):2857-65.

88. Donadieu J, Piguet C, Bernard F, Barkaoui M, Ouache M, Bertrand Y, et al. A new clinical score for disease activity in Langerhans cell histiocytosis. Pediatr Blood Cancer. 2004 Dec;43(7):770-6.

APPENDIX 1 – CLINICAL CLASSIFICATION OF LCH

Clinical forms of LCH

Disease categories:	Definitions:
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 • 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" (e.g. hematopoietic system, liver, spleen)

Definition of risk organ involvement

Hematopoietic involvement: (with or without bone marrow involvement*)	**At least 2 of the following:** • **anemia:** hemoglobin <100 g/L (<10 g/dl), infants <90 g/L (<9.0 g/dl), not due to other causes e.g. iron deficiency • **leukocytopenia:** leukocytes <4,0 x10^9/l (4,000/µL) • **thrombocytopenia:** platelets <100 x10^9/l (100.000/µL)
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 • **dysfunction** (i.e. hypoproteinemia <55 g/L, hypoalbuminemia <25 g/L, not due to other causes and/or • **histopathological findings** of active disease

*Bone marrow involvement is defined as presence of CD1a positive cells on marrow slides. The clinical significance of marrow CD1a positivity is still unclear. Hemophagocytosis may be prominent. In cases of severe progressive disease, prominent hemophagocytosis, as well as hypocellularity, myelodysplasia or myelofibrosis may be found.

** Enlargement in **cm below the costal margin** as assessed by palpation is used for definition of organ involvement.

APPENDIX 2 – GUIDELINES FOR BRAIN MRI IN LCH

The aim of cranial MRI in patients with LCH is to systematically seek neuro-degenerative involvement (cerebellum, basal ganglia, brain stem) and tumorous (hypothalamic-pituitary region, meninges, pineal gland, choroid plexus) involvement. Therefore, the MRI protocol for the examination of the brain of patients with CNS-LCH - especially for a first exploration - must be able to assess both the hypothalamic-pituitary axis and the entire brain.[38]

To meet minimal quality requirements the MRI scan must include:

- thin axial T1-weighted sequences (T1 3mm, 50% gap only for pituitary/hypothalamic regions, axial T1 5mm, 50% gap for the whole brain (to see hyperintensity in basal ganglia/dentate nuclei)
- thin coronal and sagittal T1-weighted sequences (≤3 mm slice thickness) for the hypothalamic-pituitary region
- axial T2-weighted and FLAIR sequences (≤5 mm slice thickness) over the entire brain
- contrast enhanced coronal and sagittal T1 weighted sequence brain and hypothalamic-pituitary region with parameters as indicated above, and one 5mm/50% gap sequence with fat suppression through the whole brain

Additional sequences may be used if indicated. We do not recommend using magnetization transfer contrast (MTC). However, if MTC is used, the same technique has to be used consistently, and this information has to be specified on the report.

APPENDIX 3 – ASSESSMENT OF DISEASE ACTIVITY AND TREATMENT RESPONSE

Assessment tool	Time point			
	Week 7	Week 13	Week 24	Week 52
Clinical examination	+	+	+	+
CBC + differential	+	+	+	+
Chemistry*	+	+	+	+
Urine**	(+)	(+)	(+)	(+)
Bone imaging ***	(+)	+	+	+
Imaging of other organs ****	(+)	(+)	(+)	(+)

* Total protein, albumin, bilirubin, ALT (SGPT), AST (SGOT), GGT, alkaline phosphatase, creatinine, INR/PT, APTT/PTT, fibrinogen, ESR

** Specific gravity and osmolality in an early morning sample, only in case of suspected DI on history or symptoms / signs

*** Bone imaging: all localizations involved at the last preceding evaluation to be assessed till complete healing or till residual changes stable on at least 2 examinations (>3 months). The imaging technique can vary depending on localization (x-ray, CT, MRI), but has to be consistent and comparable in a given patient over the time. Imaging of the bone lesions at week 7 is meaningful only in case of suspected progression (growing lump, pain, new locations, etc.).

**** Imaging of other organs (e.g. chest x-ray /CT, MRI of head & neck etc.) if previously indicated and still abnormal at the last previous FU or as clinically indicated.