INTERNATIONAL COLLABORATIVE TREATMENT PROTOCOL FOR CHILDREN AND ADOLESCENTS WITH LANGERHANS CELL HISTIOCYTOSIS

Published: 20-12-2013
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This study has been transitioned to CTIS with ID 2024-512676-36-00 check the CTIS register for the current data. * To decrease mortality in MS-LCH by an early switch of patients with risk organ involvement, who do not respond to front-line therapy,...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON50201

Source
ToetsingOnline

Brief title
LCH IV protocol

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Langerhans cell histiocytosis

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Kinderoncologie Nederland
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: adolescents, LCH, pediatric, treatment

Outcome measures

Primary outcome

The primary endpoints are different for the different strata, therefore listed per stratum here.

Stratum I & II: Reactivation- free survival

Stratum III: The response will be evaluated at 4-5 weeks from the initiation of the second cycle (about 9-10 weeks from start of Stratum III).

Stratum IV: To determine the overall and disease free survival at 1 and 3 years after reduced intensity conditioning hematopoietic stem cell transplantation (RIC-HSCT)

Stratum V: To study the course of ND-CNS-LCH (both radiological and clinical neurodegeneration) * To study the impact of 2-CdA on the response of isolated tumorous CNS lesions.

Stratum VI: Reactivation-free survival

Stratum VII: Cumulative incidence of specific permanent consequences (PC) e.g. diabetes insipidus (DI), growth hormone deficiency (GHD), neuropsychological impairment

Secondary outcome

The secondary endpoints are different for the different strata, therefore

listed per stratum here.

Stratum I: * Overall survival * Incidence of permanent consequences * Toxicity of treatment * The proportion of patients alive and free of disease without permanent consequences * Cumulative incidence of reactivations in risk organs

Stratum II: To determine the response rate to the combination of prednisone, vincristine and cytarabine * The proportion of patients alive and free of disease without permanent consequences (e.g. diabetes insipidus, anterior pituitary dysfunction, radiological or clinical neurodegeneration)

* To describe treatment-related toxicities * To compare reactivation rates after continuation treatment with Indomethacin vs. 6-MP/MTX.

Stratum III: Time to complete disease resolution (Non-Active Disease) - The type of subsequent intensive and/or maintenance therapy utilized

- The early and late mortality - The early and late toxicity

Stratum IV: To determine d+100 transplant related mortality, * To determine the incidence of hematopoietic recovery, and donor chimerism at d+100 and 1 year post RIC-HSCT * To determine the incidence of grades II-IV and III-IV acute GVHD, * To determine the incidence of chronic GVHD

Stratum V: To assess whether systemic therapy can be beneficial for patients with clinically manifest ND-CNS-LCH * To assess the role of 2-CdA in preventing ND-CNS-LCH in patients with isolated tumorous CNS-LCH * To study the efficacy of intravenous immunoglobulin and intravenous cytarabine in the treatment of ND-CNS-LCH (by both radiological and clinical assessment) * To assess markers of neurodegeneration and LCH activity in the spinal fluid of patients who have diabetes insipidus as well as patients with

radiologic and/or clinical signs of CNS-LCH

Stratum VI: Need for systemic therapy later during disease course * Spectrum

and cumulative incidence of permanent consequences

Stratum VII: Identify possible risk factors for PC * Assess the role of

systemic treatment in preventing PC

Study description

Background summary

LCH is a rare disease of the immune system that may affect any age group. It can affect many different organs, including the skeleton, skin, lymph nodes, liver, lungs, spleen, hematopoiesis, or central nervous system (CNS). Accordingly, the range of clinical symptoms is wide. There are two widely recognized disease extent categories: single-system LCH (involvement of a single organ or system) and multisystem LCH (involvement of 2 or more organ systems). Patients with SS-LCH of the skeleton, skin, or the lymph nodes have an excellent prognosis and are felt to need a minimum or sometimes even no treatment at all. The course of multisystem LCH (MS-LCH) is unpredictable upon diagnosis, ranging from spontaneous resolution to fulminant progression and fatal outcome. Involvement of crucial organs like the hematopoietic system, liver, or spleen has been found to herald a poor prognosis in different studies. Recent large clinical trials have shown that the response to initial treatment is a highly important prognostic factor. Patients with MS-LCH without involvement of *risk organs* have very high (>95%) probability of survival when treated with a standard regimen consisting of vinblastine and steroids. In contrast, involvement of risk organs carries the risk of unfavourable outcome. Patients with reactivations or chronic disease may experience severe permanent consequences (PC) reducing the patient*s quality of life, in particular when they affect the CNS or lungs and lead to hormone deficiencies, a neurodegenerative syndrome, lung fibrosis, etc.
The international efforts of the past 20 years have shown that combination therapy with vinblastine and prednisone is an effective therapy for MS-LCH. The previous prospective trial LCH-III confirmed this regimen as a standard regimen for MS-LCH in patients with and without risk organ involvement. It also showed that prolonged treatment in the latter group (treatment duration of 12 vs. 6 months) is superior in preventing disease reactivations. The results of this trial are encouraging and serve as a basis for the LCH-IV study design. Due to the complexity of the disease presentations and outcomes, the LCH-IV study

seeks to tailor treatment based on features at presentation and on response to treatment, leading to seven strata:
* Stratum I: First-line treatment for MS-LCH patients (Group 1) and patients with SS-LCH with multifocal bone or *CNS-risk* lesions (Group 2)
* Stratum II: Second-line treatment for non-risk patients (patients without risk organ involvement who fail first-line therapy or have a reactivation after completion of first-line therapy)
* Stratum III: Salvage treatment for risk LCH (patients with dysfunction of risk organs who fail first-line therapy)
* Stratum IV: Stem cell transplantation for risk LCH (patients with dysfunction of risk organs who fail first-line therapy)
* Stratum V: Monitoring and treatment of isolated tumorous and neurodegenerative CNS-LCH
* Stratum VI: Natural history and management of *other* SS-LCH (patients who do not need systemic therapy at the time of diagnosis)
* Stratum VII: Long-term Follow up (all patients irrespective of previous therapy will be followed for reactivation or permanent consequences once complete disease resolution has been achieved and the respective protocol treatment completed)

Study objective

This study has been transitioned to CTIS with ID 2024-512676-36-00 check the CTIS register for the current data.

* To decrease mortality in MS-LCH by an early switch of patients with risk organ involvement, who do not respond to front-line therapy, to a more intensive treatment (Stratum III or Stratum IV).
* To reduce reactivation rates and permanent consequences in MS-LCH (Group 1) through prolongation (12 vs. 24 months) and intensification (+/- 6-MP) of continuation treatment (2x2 factorial randomized trial)
* To reduce reactivation rates and permanent consequences in a subset of SS-LCH (multifocal bone or isolated *CNS-Risk* lesions (Group 2) through prolongation (6 vs. 12 months) of continuation therapy (randomized trial)
* To investigate the value of a uniform second-line therapy with PRED/ARA-C/VCR followed by randomized continuation therapy (24 months of Indomethacin vs. 6-MP/MTX) in patients with non-risk organ LCH (both nonresponders to first-line regimen and those who experience disease reactivation in non-risk organs after its completion) with respect to achievement of complete disease resolution, prevention of further reactivations and permanent consequences
* To evaluate the value of 2-CdA in patients with isolated tumorous CNS-LCH
* To evaluate whether systemic therapy with intravenous immunoglobulin (IVIG) or low dose cytarabine can achieve improvement of the neuropsychological symptoms in patients with clinically manifest neurodegenerative CNS-LCH.
* To describe the spectrum and incidence of permanent consequences in systemically treated patients, identify possible risk factors, and assess the role of systemic treatment in their prevention

* To prospectively study the natural course of SSLCH in patients who initially are not candidates for systemic therapy, with respect to disease progression, reactivations, need for medical interventions, as well as permanent consequences, at any time after diagnosis.

Study design

Clinical treatment study with a randomisation for 2 strata

Intervention

Children and adolescents with LCH need to be treated. Treatment is based on the different strata as named in the background and in the protocol. The protocol is the internationally accepted guideline for treatment of children with LCH. For 2 strata a randomisation will be performed (after consent from patient and/ or parents). In MS-LCH (Group 1) through prolongation (12 vs. 24 months) and intensification (+/- 6-MP) of continuation treatment (2x2 factorial randomized trial). In a subset of SS-LCH (multifocal bone or isolated *CNS-Risk* lesions (Group 2) through prolongation (6 vs. 12 months) of continuation therapy.

Study burden and risks

Children and adolescents with LCH need to be treated. Treatment is based on the different strata as named in the background and in the protocol. The protocol is the internationally accepted guideline for treatment of children with LCH. Nevertheless safety guidelines are reported in the protocol. There will be no extra interventions apart from the standard interventions as described in the protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

* Definitive diagnosis of Langerhans cell histiocytosis
* Age less 18 years at time of definitive diagnosis
* Met inclusion criteria for the respective stratum
* Signed written informed consent

Exclusion criteria

Exclusion criteria are stratum specific

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-01-2014
Enrollment:	85
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Indometacine 25 mg Teva, capsules
Generic name:	Indometacine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Methotrexaat Sandoz 2,5 mg, tablets
Generic name:	Methotrexaat
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Prednisolon PCH 5 mg-Tabletts
Generic name:	Prednisolon
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Puri-Nethol 50mg tablets
Generic name:	6-mercaptopurine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vinblastinsulfat Teva 1 mg/ml solution for infusion
Generic name:	Vinblastin sulfat
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	20-12-2013
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2016
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660

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Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-512676-36-00
EudraCT	EUCTR2011-001699-20-NL
CCMO	NL43352.018.13