LBL 2018 - International cooperative treatment protocol for children and adolescents with lymphoblastic lymphoma

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This study has been transitioned to CTIS with ID 2023-508101-24-00 check the CTIS register for the current data. The primary objective of the first randomized question (R1) open for allLBL patients (pts) of the core study cohort, is to evaluate...

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

Summary

ID

NL-OMON54528

Source
ToetsingOnline

Brief title
LBL 2018

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
LBL, Lymphoblastic lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: University Hospital Münster

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Adolescents, Children, Lymphoblastic lymphoma

Outcome measures

Primary outcome

• Randomization R1: Cumulative incidence of relapse with involvement of the CNS (CNS-relapse, pCICR). The time to relapse is the time from randomization to the first relapse or the date of last follow-up. Other events (non-response, progressive disease, relapse, second malignancy or death before and in CR) will be taken into account as competing events.

• Randomization R2: Estimated probability of event-free survival (pEFS). The pEFS is the time from randomization to the first event (non-response, progressive disease, relapse, second malignancy or death from any cause) or date of last follow-up.

Secondary outcome

The secondary endpoints of the trial LBL 2018 are the following:

•survival (pOS) defined as time from diagnosis to death due to any cause or to the date of last contact for patients alive.

•frequency of treatment-related toxicity and mortality overall and in specific protocol elements, randomized arms and during follow-up.

•frequency of adverse events of interest and severe adverse events overall.

•rate of evaluable patients for risk group stratification.

•cumulative incidence of relapses in association with molecular markers of the

published genetic classifier (PTEN mutations and deletions, PIK3R1, PIK3CA,

KRAS, NRAS, chromosome 6q alterations, status of TRG locus) and targeted panel.

•cumulative incidence of relapses in association with minimal residual disease

results.

Study description

Background summary

Non-Hodgkin lymphoma (NHL) is the fourth most common type of malignancy in children and
adolescents. Lymphoblastic lymphoma (LBL) accounts for about 25-35% of NHL in childhood
and adolescence. About 75-80% of patients are diagnosed with a T-cell lymphoblastic
lymphoma (T-LBL) and 20-25% with a precursor B-cell lymphoblastic lymphoma (pB-LBL).
Both LBL subtypes are treated according to the same treatment strategy. LBL share
morphological, immunophenotypic and clinical characteristics with acute lymphoblastic
leukemia (ALL).
Although the 5-year event-free-survival and overall survival for pediatric LBL patients
substantially increased during the last decades, the prognosis of relapsed patients remains
poor. On the other hand the intensive treatment regimens are accompanied by high toxicity with considerable mortality and morbidity.
The BFM treatment strategy for lymphoblastic lymphoma is based on the treatment regimen
of the ALL-BFM protocol. It consists of a 9-week induction, an 8-week consolidation and a 7-
week re-induction treatment followed by an oral maintenance up to total therapy duration of 2
years. Best results were achieved in the trial NHL-BFM 90 with pEFS of 90%.
The subsequent clinical trial EURO-LB 02 was run by the European Inter-group Co-operation
on childhood and adolescent NHL (eicnhl). For the trial EURO-LB 02 it was accepted that the treatment regimen of the trial NHL-BFM 90 should serve as the reference arm of the study.
The 90% pEFS rate for T-LBL shown in study NHL-BFM 90 could not be replicated

mainly due to more toxic deaths and CNS relapses.
The conclusion of the international co-operative trial is that dexamethasone in induction may
prevent CNS relapse more effectively than prednisone but produces a higher burden of
toxicity. Therefore in this study the duration of dexamethasone exposure is limited to 14 days to reduce the risk of toxicities. It was decided to evaluate prospectively whether a short 14-day dexamethasone arm (experimental arm) compared to standard 21-day prednisone (standard arm) in the induction phase protocol Ia may reduce CNS related relapses.
It is agreed that prognostic parameters are most urgently needed for pediatric LBL patients to
prevent overtreatment and subsequent acute and long term toxicities as e.g. osteonecrosis in
low risk patients. And on the other hand, prognostic parameters identifying high risk patients
allowing subsequent treatment intensification to prevent often fatal relapses are highly
warranted. Molecular studies and an international meta-analysis have led to a new stratification system based on the mutational profile of distinct genes in (NOTCH1 and FBXW7) in patients with T-LBL. The aim of introducing this stratification system in parallel with stratification according to CNS status, immunophenotype and stage of disease is to improve the pEFS and OS and to reduce the risk of CNS-related relapses in pediatric patients with LBL.
Therefore a new stratification system based on NOTCH1 and FBXW7 mutational status for T-LBL and stage of disease for pB-LBL is introduced in this study
Additionally, in the medium term, patients with T-LBL may not only benefit from the proposed risk group stratification system including genetic markers but also of the identification of potential additional prognostic molecular markers that can be added in subsequent trials.

Study objective

This study has been transitioned to CTIS with ID 2023-508101-24-00 check the CTIS register for the current data.

The primary objective of the first randomized question (R1) open for all LBL patients (pts) of the core study cohort, is to evaluate whether the cumulative incidence of relapses in the central nervous system can be decreased by substituting prednisone (60 mg/m²/d for 21 days plus a 9 day tapering) (standard arm, SA) by dexamethasone (10 mg/m²/d for 14 days without tapering) (experimental arm, EA) in induction therapy.
The primary objective of the second randomized question (R2) open for high-risk pts of the core study cohort, is to test whether the probability of pEFS can be improved by an intensified treatment arm (EA) compared to the standard treatment arm (SA). In the EA pts receive 2 additional doses of PEG asparaginase during protocol Ib* and an intensified

protocol M consisting of one course for high-risk (HR) ALL (HR-1'), followed by one standard high-dose methotrexate (MTX) course, followed by another intense course for HR ALL (HR-2') and a second standard high-dose MTX course.

Study design

International inter-group multi-centre open-label randomized prospective clinical trial

Intervention

N.A.

Study burden and risks

De primaire reden voor randomisatie 1 (prednison versus dexamethason) is het verminderen van het aantal CNS recidieven. Inductie van dexamethason kan gepaard gaan met een verhoogd risico op behandeling gerelateerde morbiditeit (infecties, hematologische toxiciteit, hepatische toxiciteit) en mortaliteit. Daarom is de duur van blootstelling aan dexamethason beperkt tot 14 dagen om het risico op toxiciteit te verminderen. De deelnemende groepen gaan ervan uit dat de potentiële voordelen van dexamethason in dit onderzoek opwegen tegen de potentiële risico's die aan studieparticipatie zijn verbonden.

De primaire reden voor randomisatie 2 met behandelintensificatie voor hoog risicopatiënten met LBL via de introductie van ALL hoog risico kuren in het geïntensiveerde protocol M is het verbeteren van de event-free survival en overall survival volgens de gevestigde ALL-BFM behandelstrategie voor hoge risicopatiënten. Vanwege de relevante toxiciteit van behandelplannen met 3 tot 6 opeenvolgende hoog risicovolle kuren waargenomen bij ALL-patiënten met een hoog risico, is overeengekomen om 2 hoge risicokuren in het protocol M te introduceren, maar om twee standaardkuren met hoge dosis methotrexaat van protocol M te behouden in de LBL 2018 studie. Potentiële risico's zijn een toename van behandeling gerelateerde morbiditeit en mortaliteit, evenals vertragingen in de behandeling. Verbetering van de overleving bij hoog risicopatiënten zou echter de overweging van deze intensievere behandeling kunnen rechtvaardigen.

Een ander beoogd voordeel van de LBL 2018 studie met de prospectieve validatie van de nieuw geïntroduceerde risicogroep stratificatie is om de behandeling aan te passen aan het individuele risico op recidief. Op de middellange termijn kan dit een verdere verlaging van de behandelingsintensiteit mogelijk maken bij patiënten met een laag risico die de acute en langdurige toxiciteit bij deze patiënten verminderen.

Contacts

Public
University Hospital Münster

Albert Schweitzer Campus 1
Münster 48149
DE
Scientific
University Hospital Münster

Albert Schweitzer Campus 1
Münster 48149
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

Patients meeting the following criteria are eligible to the study (inclusion criteria):
•newly diagnosed lymphoblastic lymphoma
•age <18 years at diagnosis
•patient enrolled in a participating center
•written informed consent of patient (>14 years of age or according to local law and regulation) and parents to trial participation and transfer and processing of data
•Willingness of patients and the investigator/pathologist to provide adequate

slides/blocks for reference (molecular)pathology and international pathology panel and/or fresh or fresh frozen samples for genetic risk group stratification if these samples are available after standard diagnostic procedures

Exclusion criteria

Patients meeting the following criteria are not eligible to the study (exclusion criteria):
•lymphoblastic lymphoma as secondary malignancy
•non-lymphoma related relevant medical, psychiatric or social conditions incompatible with trial treatment including among others :
- prior organ transplant
- severe immunodeficiency
- demyelinating Charcot-Marie Tooth syndrome
- serious acute or chronic infections, such as HIV, VZV and tuberculosis
- urinary tract infection, cystitis, urinary outflow obstruction, severe renal impairment (e.g. creatinine clearance less than 20 ml/min)
- severe hepatic impairment (bilirubin >3 times ULN, transaminases >10 times ULN)
- myocardial insufficiency, severe arrhythmias
- ulcers of the oral cavity and known active gastrointestinal ulcer disease
- known hypersensitivity to any IMP and to any excipient (listed in section 6.1 of the respective SmPC)
•steroid pre-treatment with >= 1 mg/kg/d for more than two weeks during the last month before diagnosis
•vaccination with live vaccines within 2 weeks before start of protocol Treatment
•treatment started according to another protocol or pre-treatment with cytostatic drugs (except INITIAL EMERGENCIES, see page 73)
•participation in another clinical trial that interferes with the protocol, except NHL-BFM Registry 2012 and trials with different endpoints, involving aspects of supportive treatment, which can run parallel to LBL 2018 without influencing the outcome of this trial (e.g. trials on antiemetics, antibiotics, strategies for psychosocial support)
•evidence of pregnancy or lactation period
•sexually active adolescents not willing to use highly effective contraceptive method (pearl index < 1) until 12 months after end of cytostatic therapy

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:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-06-2021
Enrollment:	42
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cytarabine
Generic name:	Cytarabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Daunorubicin
Generic name:	Daunorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	31-10-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2023-508101-24-00
EudraCT	EUCTR2017-001691-39-NL
CCMO	NL67395.078.19