International Study for Treatment of High Risk Childhood Relapsed ALL

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Primary objectives: Improvement of CR2 rates after induction with ALL R3 with bortezomib versus without bortezomib in HR relapsed ALL patients Secondary objectives: Improvement of Event Free Survival (EFS) and overall survival (OS) rates...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON26156

Source
Nationaal Trial Register

Brief title
IntReALL HR

Condition

- Leukaemias

Synonym
Relapsed ALL

Health condition
Relapsed High-Risk childhood leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Charité University Medicine Berlin
Source(s) of monetary or material Support: DCOG

Intervention

Explanation

Outcome measures

Primary outcome
Randomized induction trial:

*Rates of CR2 with standard chemotherapy + Bortezomib (Arm B) compared with standard chemotherapy (Arm A), quantified by cytology

Secondary outcome
*Three years EFS and OS

*Rate of patients reaching HSCT

*MRD rates post-induction and pre-HSCT

*Prognostic relevance of MRD pre HSCT, CR2 and MRD rates during consolidation

*Toxicity of randomized arms

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Study description

Background summary
Although survival of children with acute lymphoblastic leukemia (ALL) has considerably improved over the past few decades, relapsed ALL remains a leading cause of mortality in children with cancer. Risk has been defined by the International BFM Study Group (I-BFM-SG) based on duration of first remission, immunophenotype of malignant clone, and site of relapse. Patients classified as high risk (HR) by these criteria have poor response rates to standard induction therapy, high rates of subsequent relapse and require an allogeneic hematopoetic stem cell transplantation (allo-HSCT) for consolidation of 2nd remission. Over the last decade members of the I-BFM-SG have investigated the use of different combinations of conventional cytotoxic agents. Even with allo-HSCT, none of these approaches have improved outcome above 40%. Therefore, for HR patients there is a need to investigate the curative potential of new agents combined with systemic therapy.

The proteasome inhibitor bortezomib has shown synergistic activity with acceptable toxicity when combined with corticosteroids, anthracyclines and alkylating agents in adult patients

with cancer as well as with dexamethasone, doxorubicin, vincristine and PEG-asparaginase in children with refractory or relapsed ALL. In the I-BFM-SG IntReALL HR 2010 study, the potential of Bortezomib combined with a modified ALL R3 backbone as induction regimen for HR patients to improve CR2 rates will be investigated in a randomized phase II design. Induction is followed by conventional intensive consolidation.

Study objective

Primary objectives:

Improvement of CR2 rates after induction with ALL R3 with bortezomib versus without bortezomib in HR relapsed ALL patients

Secondary objectives:

Improvement of Event Free Survival (EFS) and overall survival (OS) rates

Improvement of minimal residual disease (MRD) reduction after induction with versus without bortezomib

Improvement of MRD load prior to SCT

Increasing the proportion of HR patients reaching SCT

Prognostic relevance of MRD pre SCT

Improvement of CR2 and/or MRD rates during consolidation

Toxicity of induction with versus without bortezomib

Study design

The IntReALL HR 2010 trial is an inter-group, international multi-centre, treatment optimization

trial. It contains the following treatment arms:

- induction: prospective, randomized, adaptive, open label phase II trial comparing arm A

(modified ALL R3) versus arm B (modified ALL R3 + bortezomib).

- post-induction single arm observational trial with intensive multidrug chemotherapy courses

HC1 (modified AIEOP-BFM ALL 2009 HR1), HC2 (modified HR3)

- a third post-induction chemotherapy block HC3 (modified AIEOP-BFM ALL HR2) may

optionally be given within the IntReALL HR 2010 trial or used as standard comparator for an

investigational window trial

- all patients in morphological CR2 will be subjected to allogeneic HSCT

- termination of the trial after completion of the 2nd or 3rd consolidation block before investigational window trial and/or allogeneic HSCT. Follow-up will be done until reaching

secondary EFS / OS endpoints.

- patients with insufficient treatment response (MRD ≥ 10-3 after induction) may be allocated to

individualized consolidation therapy based on individual biologic features of the leukemia, if such approaches are available

Intervention
Bortezomib (Velcade)

Study burden and risks
Participation in the trial does not result in additional investigations as compared to the standard treatment of children with relapsed ALL.

The risk of increased toxicity by adding Bortezomib to the standard ALL-R3 remission induction is considered to be low and will be closesly monitored by the pharmacovigilance system established within the IntReALL group. Strict stopping rules apply. The induction randomization implies realistic potential to improve remission, EFS and at the end cure rates in this unfavourable patient group with an acceptable and closely monitored risk for increased toxicity.

Contacts

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Eligibility criteria

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

Inclusion criteria

• Morphologically confirmed diagnosis of 1st relapsed precursor B-cell or T-cell ALL

• Children less than 18 years of age at date of inclusion into the study

• Meeting HR criteria (any T BM relapse, early/very early isolated BM relapse, very early isolated/combined extramedullary relapse)

• Patient enrolled in a participating centre

• Written informed consent

• Start of treatment falling into the study period

• No participation in other clinical trials 30 day prior to study enrolment that interfere with

this protocol, except trials for primary ALL

Exclusion criteria

• BCR-ABL/ t(9;22) positive ALL

• Pregnancy or positive pregnancy test (urine sample positive for â-HCG > 10 U/l)

• Sexually active adolescents not willing to use highly effective contraceptive method (pearl index <1) until 12 months after end of anti-leukemic therapy

• Breast feeding

• Relapse post allogeneic stem-cell transplantation

• Neuropathy > II°

• The whole protocol or essential parts are declined either by patient himself/herself or the respective legal guardian

• Objection to the study participation by a minor patient, able to object

• Any patient being dependent on the investigator

• No consent is given for saving and propagation of pseudonymized medical data for study reasons

• Severe concomitant disease that does not allow treatment according to the protocol at the investigator’s discretion (e.g. malformation syndromes, cardiac malformations, metabolic disorders)

• Subjects unwilling or unable to comply with the study procedures

• Subjects who are legally detained in an official institute

Study design

Design

Study phase:	2
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):	19-10-2020
Enrollment:	15
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Approved WMO

Date:	10-04-2020
Application type:	First submission
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

ID: 49335
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL5524
NTR-old	NTR7090
EudraCT	2012-000810-12
CCMO	NL67089.041.19
OMON	NL-OMON49335

Study results