International collaborative treatment protocol for infants under one year with KMT2A-rearranged acute lymphoblastic leukemia or mixed phenotype acute leukemia

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This study has been transitioned to CTIS with ID 2022-502503-30-00 check the CTIS register for the current data. The primary objective is to improve the outcome (in terms of event-free survival (EFS) as the primary endpoint) of newly diagnosed KMT2A...

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

Summary

ID

NL-OMON51982

Source
ToetsingOnline

Brief title
Interfant-21

Condition

- Leukaemias
- Leukaemias

Synonym
Leukemia; acute lymphoblastics leukemia (ALL)

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Ministerie van OC&W,Amgen,Amgen;Maxima Foundation

Intervention

Keyword: blinatumomab, Infants under 1 year, KMT2A-rearranged acute lymphoblastic leukemia, Treatment protocol

Outcome measures

Primary outcome

The primary endpoint is Event Free Survival, defined as the time from diagnosis to resistance to induction, relapse, death from any cause or second malignancy (whichever occurs first), or time to last follow-up (censored) for patients without events.

Secondary outcome

Secondary endpoints

1. OS is defined as the time from the date of diagnosis to death from any cause. Patients who are alive will be censored at the date of last follow up. OS will be estimated for the entire study co-hort and according to risk group

2. The endpoints for analysis by risk group will be EFS, cumulative incidence (or percentage) of resistance to induction, cumulative incidence of relapse (CIR), death in complete remission (CR) and second malignancy.

3. Outcome for the entire study cohort and according to risk group will be evaluated in terms of the protocol specific definition of EFS follows: the time from diagnosis to, resistance to proto-col, relapse, death from any cause or second malignancy (whichever occurs first), or time to last follow-up for

patients without events. Cumulative incidence (or percentage) of resistance,

CIR, death in CR and second malignancy will also be estimated.

4. MRD response as defined in the protocol and frequencies of MRD levels

5. Proportion of CD19 negative relapses in the entire study cohort and

according to risk group

6. Proportion of myeloid lineage switches in the entire study cohort and

according to risk group

7. Proportion of grade >=3 adverse event (AEs) during the blinatumomab

course(s). Proportion of adverse events of special interest (AESIs) and serious

adverse events (SAEs) in all protocol phases.

8. Proportion of grade >=2 cardiac disorders at 2 and 5 years after diagnosis

9. OS after first relapse, defined as the time from first relapse to death from

any cause, in the entire study cohort and according to risk group

Study description

Background summary

Infant acute lymphoblastic leukemia (ALL) is a rare disease and comprises about 4% of childhood ALL. Whereas the outcome of older children with ALL has improved to >90% event-free survival (EFS), infants with ALL have a poor prognosis.
Infant ALL is characterized by a high frequency (~75%) of abnormalities in the chromosome 11q23 that affect the histone lysine methyltransferase 2A (KMT2A) gene, formerly known as mixed lineage leukemia (MLL) gene. KMT2A-rearrangements (KMT2A-r) occur in only 2% of older children with ALL. KMT2A-r is associated with poor outcome.
nfant ALL has a very immature CD19-positive B-cell phenotype (pro-B ALL) without CD10 expression, and a high tumor load at diagnosis. Infant ALL cells are more resistant to chemotherapy than ALL cells of older children, but are sensitive in vitro to cytarabine. Therefore the Interfant treatment protocol contains more cytarabine than a standard ALL regimen for older children.

Unfortunately, treatment outcome has not significantly improved in the last few decades. This supports the need for improvement of upfront treatment with innovative strategies directed against novel targets.

The Interfant-21 protocol will implement several major changes to the Interfant-06 backbone (see section study design)

Study objective

This study has been transitioned to CTIS with ID 2022-502503-30-00 check the CTIS register for the current data.

The primary objective is to improve the outcome (in terms of event-free survival (EFS) as the primary endpoint) of newly diagnosed KMT2A-rearranged (KMT2A-r) infant acute lymphoblastic leukemia (ALL) compared with the historical results of the Interfant06 protocol.

The secondary objectives are:
1. To estimate overall survival (OS) and compare it with corresponding historical results of the Interfant-06 protocol, in the whole study and by risk group.
2. To determine outcome (in terms of secondary endpoint 2) according to risk group and com-pare it with corresponding historical results of the Interfant-06 protocol.
3. To determined outcome (in terms of secondary endpoint 3) taking into account the protocol-specific definition of resistance.
4. To assess the response to different treatment phases in term of minimal residual disease (MRD) response.
5. To evaluate the incidence of CD19 negative relapses
6. To evaluate the incidence of myeloid lineage switches
7. To describe the toxicity associated to each treatment phase.
8. To describe long term cardiotoxicity
9. To evaluate survival after relapse, overall and by risk group

Study design

International multicenter open-label non-randomized phase 3 clinical trial conducted in the Interfant network. This protocol is a master protocol which will be implemented in all participating countries and sites, with a number of sub-studies that will only be performed in a restricted number of countries and sites (based on feasibility and interest). This will be documented in a sub-study manual, and participation in these studies will be clearly documented in the submission package in each country/site. The objectives and design of the sub-studies are provided in the sub-study protocols.

The Interfant-21 protocol will implement several major changes to the Interfant-06 backbone, listed below, and in more detail in the following paragraphs:
• Less stringent adaptation of age-based dose reduction guidelines.
• Allocation to lymphoid or myeloid consolidation therapy, based upon EOI MRD in MR patients.
• One cycle of blinatumomab following induction in all patients.
• A second cycle of blinatumomab will replace MARMA in MR patients with a good response af-ter the first cycle of blinatumomab.
• All HR patients and MR patients with insufficient MRD response will be eligible for for allogene-ic hematopoitetic stem cell transplantation (HSCT) as soon as they have become MRD nega-tive or at least < 0.01%.
• HR patients and MR patients with insufficient MRD response after will be eligible for experi-mental therapy, such as CAR T-cell therapy, which cab be on a separate trial, as a bridge to HSCT.

The Interfant-21 study will not include a randomization because of the rarity of the disease and the unsatisfactory stable outcome of treatment without blinatumomab in the Interfant-99 and Interfant-06.

Intervention

1 or 2 cycles blinatumomab

Study burden and risks

Whereas the outcome of older children with ALL improved > 85%, infants with KMT2A-r ALL have an EFS of less than 40%, hence there is clear medical need in this specific population.

1) Risk and benefits of addition blinatumomab

Within the Interfant consortium a phase 2 clinical trial with blinatumomab was performed, in which blinatumomab was given after induction. The results showed the same favorable safety profile and response, as in adults and in older children (vdSluis #361 ASH2021). The 1years EFS was 90.0%(SE 5.5) , which was remarkable better than Interant-06 (1-year EFS 54.8%(SE 2.3)). Two randomized phase 3 trials in high-risk relapsed pediatric ALL also shown the superiority of one or two cycles of blinatumomab in consolidation when randomized against chemotherapy, due to both higher disease clearance as well as reduced toxicity. Therefore blinatumomab will be added to the Interfant-06 back-bone for all patients.
To potentially further increase efficacy and decrease treatment related toxicity, medium risk patients with a good response to one cycle of blinatumomab will receive a second cycle of blinatumomab re-placing the

conventional chemotherapy block MARMA. There may be a higher relapse risk if intensity of conventional chemotherapy is decreased, but this will be mitigated by including only those patients who have obtained a good response to the first cycle of blinatumomab. Moreover, this strategy is also based on the data in older children with relapsed ALL as referenced above. Outcome will be monitored by the DSMC to alert the Interfant Study Team in case of any evidence of deviation from the historical results of Interfant06. Stopping guidelines are included in the study, based on the number of events to further mitigate this risk.
Taken together, we anticipate that the addition of blinatumomab will benefit patients and outweighs the risk of treatment with an investigational agent

2) Risk and benefits of other changes compared to Interfant-06.

a. Less stringent adaptation of age-dependent drug reduction
Compared to the former Interfant-06 protocol, infants will get less stringent adaptation of age-dependent drug reduction. Thus all infants will receive higher doses of chemotherapeutic drugs compared to Interfant-06. For decades Japanese trials (MLL-96 and MLL-10) have used less stringent adaptation of age-dependent drug reduction and in these trials not more treatment related mortality was reported with this approach. However higher molecular remission rates at EOI were achieved and higher EFS was observed.

b. Allocation to myeloid consolidation therapy based on high EOI MRD in medium risk patients
Patients with high EOI MRD will receive more intensive, myeloid style, consolidation therapy, which is associated with more treatment related toxicity and mortality (TRM 4.7%, versus 0% in lymphoid style consolidation phase). However the survival of patients with high EOI MRD was improved by >20% in Interant-06 (6-y DFS 45.9% with myeloid style consolidation versus 23.2% with lymphoid style consolidation) in patients with high EOI MRD. So the risk of higher toxicity and TRM is accepted in a sub-group of patients with very poor outcome, to increase survival.

c. Broader and earlier eligibility for HSCT
All HR patient and MR with insufficient MRD response will be eligible for HSCT as soon as they have become MRD negative or at least < 0.01%. In Interfant-06 approximately 50% of HR patients had an event before the scheduled HSCT, of which 41% due refractory disease or relapse. Therefore HR and eligible MR patients will be eligible for HSCT as soon as they have become MRD < 0.01% to avoid relapse before HSCT. TRM of HSCT was approximately 14.4% in Interfant-06 (JCO 2019 Pieters), however in recent years the TRM of HSCT has decreased to approximately 5% (ref Pieters, JCO 2019). Therefore, the benefit of HSCT to avoid a relapse seems to outweigh the risks of HSCT.

d. Experimental targeted therapies in an investigation window
High-risk (HR) patients and medium risk patients with insufficient MRD response

after induction and blinatumomab have very poor outcomes with conventional chemotherapy, therefore these patients will be eligible for experimental therapy in separate trials in an investigational window, as a bridge to HSCT. The risk and benefits of these trials will be given in the protocols of these trials.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

1. Patients with newly diagnosed B- precursor ALL or B-cell MPAL according to the WHO classification of tumours of haematopoietic and lymphoid tissues (revised 4th edition 2017, with KMT2A-rearrangement.
2. <= 365 days of age at the time of diagnosis of ALL.
3. Written informed consent of the parents or other legally authorized

guardian of the patient according to local law and regulations.

Exclusion criteria

1. KMT2A-germline patients.
2. T-ALL.
3. Age > 365 days at the time of diagnosis.
4. Relapsed ALL.
5. Treatment with systemic corticosteroids (equivalent prednisone >10 mg/m2/day) for more than one week and/or any chemotherapeutic agent in the 4-week interval prior to diagnosis. Patients who received corticosteroids by aerosol are eligible for the study.

Additional exclusion criteria for blinatumomab:
1. CD19 negative B-precursor ALL at diagnosis
2. CNS involvement (CNS2/CNS3/TLP+ status) at the EOI. Patients with CNS disease at the time of diagnosis are eligible if CNS1 status is achieved prior to the start of the first blinatumomab cycle (lumbar puncture at ~day 33 of induction).
3. Proven hypersensitivity to the active substance or any of the excipients in blinatumomab.
4. Patients who have received a live vaccine 28 days prior to blinatumomab administration or plan to receive a live vaccine prior to B-cell recovery after the last dose of blinatumomab.

If exclusion criteria for blinatumomab are met, the patient should be treated according to the protocol but without blinatumomab.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-01-2023
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Blincyto
Generic name:	Blinatumomab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-05-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-09-2022
Application type:	First submission
Review commission:	METC NedMec

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	CTIS2022-502503-30-00
EudraCT	EUCTR2021-000213-16-NL
ClinicalTrials.gov	NCT05327894
CCMO	NL76396.041.22