A pilot study to test the feasibility, safety and efficacy of the addition of the BiTE antibody Blinatumomab to the Interfant-06 backbone in infants with MLL-rearranged acute lymphoblastic leukemia. A collaborative study of the Interfant network.

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

Summary

ID

NL-OMON49535

Source
ToetsingOnline

Brief title
Blinatumomab in infant ALL

Condition

- Leukaemias

Synonym
Acute Lymphoblastic Leukemia (ALL), Leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Amgen Research GmbH, Uxbridge, Verenigd Koninkrijk,Go4Children;Mammoet B.V.;Amgen (drug supply)

Intervention

Keyword: acute lymphoblastic leukemia, blinatumomab, pediatric patients, phase 2

Outcome measures

Primary outcome

Incidence of clinically relevant toxicities defined as any toxicity that is

possibly or definitely attributable to blinatumomab AND results in permanent

discontinuation of blinatumomab OR death.

Secondary outcome

Toxicity/feasibility:

1. Incidence and severity of (serious) adverse events, independently to

relationship with blinatumomab

2. Number of treatment interruptions due to toxicity occurring during

blinatumomab

3. Proportion of patients that receive a full course (4 weeks) of blinatumomab

4. Incidence and severity of key safety parameters till start of

maintenance and during long-term follow-up

Activity/Efficacy:

5. MRD response at the following time-points: TP2 d33 (end of induction),

TPblina1 d15 (after initial 15 days of blinatumomab) and TPblina2 d29 (after

the complete course of blinatumomab)

6.. MRD response after Protocol IB: TP2 d33 (end of induction) and TP4 (end of

Protocol IB)

7. Proportion of MR patients with MRD > 5x10-4 before OCTADAD (indication for

SCT)

8. cCR/CR and 6 months post-induction EFS and the long-term EFS and OS

Pharmacokinetics:

9. Steady state concentration of blinatumomab (Css)

Study description

Background summary

Acute lymphoblastic leukemia (ALL) in infants is a rare disease and comprises about 4% of childhood ALL. In contrast to greatly improved prognosis (> 85% EFS) in older children with ALL, have newly diagnosed children (<1 year) with ALL a significantly worse prognosis with an EFS of 47%. Especially the children with a mixed lineage leukemia- rearrangement (MLL-R), which is found in 80% of patients, have a worse prognosis than older children with ALL. Relapses occur early and survival after relapse is only 20%. Therefore, the upfront treatment must be improved and require these patients innovative strategies against novel targets.

Blinatumomab is a bispecific single-chain antibody designed to link CD19 expressing B cells and CD3+ T cells resulting in T cell activation and a cytotoxic T cell response against the CD19 expressing cells. In vitro data indicate CD19+ lymphoma and leukemia cell lines to be extremely sensitive to blinatumomab-mediated cytotoxicity. Blasts in infant ALL express CD19.

Blinatumomab belongs to a new class of bispecific antibody constructs called bispecific T-cell engagers (BITE®). BITEs have been designed to direct T-effector memory cells towards targets cells. It resembles standard cytotoxic T-lymphocyte activation. Because blinatumomab targets cells that express CD19,

a marker solely expressed by B cells, including precursor B-ALL cells its cytotoxicity is highly selective. Blinatumomab recruits and activates T-cells via CD3. In vitro these activated T-cells induce target cell lysis ranging between 10-100 pg/mL, showing that blinatumomab is an extremely potent molecule.3
Blinatumomab needs both the presence of CD19 positive target cells and T-cells for its cytotoxic activity.

Also, clinical studies show that blinatumomab is effective and well tolerated in children and adults with ALL who are already pre-treated with intensive chemotherapy. Our hypothesis is that one treatment blinatumomab can be safely added to the Interfant-06 backbone and will reduce the MRD values.

The toxicity and efficacy data from this pilot study with blinatumomab will be used to assess whether blinatumomab will be examined more extensive (eg, in a randomized study) in the new joint protocol of the COG / JPLSG and Interfant group.

Study objective

The primary objective of the study is to assess the safety of 1 course of blinatumomab added to the Interfant-06 backbone in infants with newly diagnosed ALL.

The secondary objectives are:
• to assess the feasibility
• to define the preliminary response rate of these regimens
• to assess pharmacokinetics of blinatumomab in infants.

Study design

It is a prospective, open-label, non-randomized, international multicenter pilot study conducted within the Interfant study group. This is a collaborative network that consists of all major European study groups and several large pediatric oncology study groups outside Europe. This pilot study will be conducted in selected centers with experience with blinatumomab in Europe and Australia and will be used to test the feasibility of adding one course of blinatumomab to the standard arm (IB) of the Interfant-06 protocol. Blinatumomab will be administered for 4 weeks immediately after induction treatment (figure 2).
Infants with ALL are treated according to the current standard of therapy, which is the Interfant-06 protocol. The only intervention will be the addition of 1 course of blinatumomab.

This study will not include a randomized question because of the rarity of the disease and the unsatisfactory outcome of a control arm without blinatumomab.

Moreover, the main objective is to assess the safety and feasibility of a blinatumomab course in the Interfant-06 backbone. As to the secondary aim concerning the evaluation of efficacy of this new schedule, a historical comparison with the MRD and EFS data of the Interfant-06 protocol will be performed.

The toxicity and safety data of this pilot study will directly influence the drug choice and dose schedule given to infants in the worldwide future collaborative COG/JPLSG/Interfant group trial, where a large number of patients will allow to address randomized questions.

See also figure 2. Treatment schedule in protocol

Intervention

The investigational product is blinatumomab. Blinatumomab will be manufactured, packaged labelled and distributed by Amgen Inc.
The Summary of Product Characteristics contains detailed information regarding the presentation, storage, preparation, and administration of blinatumomab. In addition, preparation and administration guidelines for this specific study population will be provided.
Blinatumomab is added to the Interfant-06 backbone, however the chemotherapy prescribed according to the Interfant-06 protocol and the intrathecal therapy at day 15 are standard of care and commercially available, and will not be provided or reimbursed by the sponsor.

Study burden and risks

Possible risks and burden related to the study

In 2014, the US Food and Drug Administration (FDA) granted accelerated approval for blinatumomab (BLINCYTO, Amgen Inc.) for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. In 2015 it has been approved by the European Medicines Agency (EMA) for adults and in August 2018 for children. In the EU and US, blinatumomab has been approved for the treatment of adults with Philapdelphia negative B- ALL in first or second CR with positive MRD.
Blinatumomab is added as an extra course in the Interfant-06 treatment protocol. This increases the risk of blinatumomab related side effects. The most important and majority of the side effects are observed in the first week of treatment, during this time the most intensive monitoring is required. Medically important toxicities are: 1) Neurological adverse events 2) Cytokine release syndrome (CRS) 3) Immune suppression, caused by decreased immunoglobulins and neutropenia.
Neurological events are mainly described in adult patients, no increased side effects with the combinations of intrathecal therapy and blinatumomab have been

seen in the pediatric study, however neurological AEs will be closely monitored and dose modifications and stopping rules are defined in the current study.
CRS was dose limiting in children with relapsed/refractory ALL when used as induction treatment. Patients with less disease burden, as in patients after induction treatment, are expected to experience less side effects.
The decreased immunoglobulins can be supplemented with intravenous immunoglobulins. In general, these side effects can be managed by standard supportive care. All R/R pediatric ALL patients in the phase II part of the study experienced AEs, mostly flu-like symptoms. AEs regardless of causality were pyrexia (74%), anemia (33%), nausea (31%), headache (28%), hypertension (26%), and cough (21%), increased alanine aminotransferase (18%), increased aspartate aminotransferase (18%), and febrile neutropenia (15%). CRS occurred in three (8%) patients.
Another possible risk is that blinatumomab is ineffective. Strict stopping rules are defined to monitor the response during blinatumomab treatment section 5.5.3. In case of disease progression patients will continue with ADE/MAE courses of the Interfant-06 protocol.
Patients need to be admitted for 4 days to 4 weeks, and 2 extra bone marrow punctures and 2 lumbar punctures are performed. For the PK analysis 2 blood samples (2 ml) are taken. Blood samples are taken from central venous line and are often part of SOC in the treatment of infants with ALL, who need a very intensive treatment, necessitating close monitoring of safety laboratory parameters. Volumes of blood will be minimized as appropriate for this pediatric population.

Possible benefits related to the study

Whereas the outcome of older children improved to >85% EFS, infants with ALL have a less than 50% EFS. Especially those with MLL-R, which is found in 80% of the infants, have a worse outcome than older children with ALL. Relapses occur early and survival after relapse is only 20%. The current Interfant-06 protocol did not significantly improve the outcome of infant ALL. These infants might benefit from innovative strategies directed against novel targets. Blinatumomab as monotherapy has shown complete remissions in CD19 positive relapsed/refractory ALL and is also effective in MRD positive patients. In the pediatric phase II studies in heavily pre-treated R/R ALL patients one third of patients had CR, mostly after the first course.
In the current Interfant-06 protocol MR patients who have MRD levels =/ > 10-4 by PCR at the start of OCTADAD are eligible for allogenic SCT. When more patients achieve a MRD level <10-4 before OCTADAD less patients need an allogenic SCT, potentially reducing the toxicity and treatment related mortality of an allogenic SCT.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Patients must be treated according to Interfant-06 backbone; 2. Patients must have newly diagnosed, CD19 positive, B-precursor acute lymphoblastic leukemia; 3. Morphological verification of the diagnosis, confirmed with immunophenotyping; 4. <= 365 days of age at time of diagnosis of ALL; 5. > 28 days of age at start of blinatumomab administration; 6. MR and HR patients according to risk stratification of the Interfant-06 protocol, thus including all MLL-rearranged and MLL not-evaluable patients (these latter are stratified and treated according to MR); 7. M1 or M2 bone marrow after induction (~day 33). If the peripheral blood shows pancytopenia at day 33 it is justified to postpone the bone marrow puncture according to the Interfant06 protocol. If the bone marrow at day 33 is hypocellular and one is therefore unable to determine M1 or M2 status, then the bone marrow puncture should be repeated; 8. Written

informed consent from parents or guardians.

Exclusion criteria

1. Biphenotypic ALL; 2. Mature B-ALL; 3. Presence of t(9;22) (q34;q11) or BCR-ABL fusion transcript; 4. M3 marrow after induction; 5. Patients with Down syndrome (because of increased toxicity of conventional chemotherapy); 6. Clinically relevant CNS pathology requiring treatment (eg unstable epilepsy); 7. Evidence of CNS involvement of ALL (CNS2 or CNS3) at the end of induction. Subjects with CNS disease at the time of diagnosis are eligible if a CNS1 status is obtained prior to enrolment (lumbar puncture at ~day 29 of induction, see definitions CNS status in Appendix D in the protocol); 8. Known infection with human immunodeficiency virus (HIV); 9. Known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing.
Exclusion criteria before start (-d3) of blinatumomab: 1. Peripheral neutrophils <0.5 x 109/l and WBC <2 x109/l (for M1 marrow only, with a maximum delay of 2 weeks. Patients with M2 bone marrow will not recover their blood counts and can start as soon as the other inclusion criteria are met); 2. Peripheral platelets < 50 x 109/L (for M1 marrow only with a maximum delay of 2 weeks. Patients with M2 bone marrow will not recover their blood counts and can start as soon as the other inclusion criteria are met); 3. Creatinine > 1.5 X ULN, based on the normal ranges for age and gender of the local Laboratories; 4. Total bilirubin > 3 x ULN unless the patient has documented Gilbert Syndrome; 5. Chemotherapy related toxicities that have not resolved to <= grade 2; 6. Symptoms and/or clinical signs and/or radiological and/or sonographic signs that indicate an acute or uncontrolled chronic infection, any other concurrent disease or medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	31-07-2018
Enrollment:	8
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:	11-07-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-02-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	24-04-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2023
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

ID: 24025
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2016-004674-17-NL
CCMO	NL59901.078.17
Other	NL5993 (=NTR6359)