Blinatumomab in infant ALL

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Blinatumomab may represent an additional therapeutic option for patients with infant ALL, who have an unmet need for treatment options that improve efficacy and/or have improved safety profile. The expected benefit will be improved efficacy of...

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24025

Source
NTR

Brief title
Blinatumomab in infant ALL

Health condition

acute lymphoblastic leukemia (ALL) Acute lymfatische leukemie (ALL)

Sponsors and support

Primary sponsor: Princess Maxima Center for Pediatric Oncology
Source(s) of monetary or material Support: Go4 Children
Mammoet
Amgen

Intervention

Outcome measures

Primary outcome

Primary endpoint 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

Secondary endpoints
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 at the following time-points: 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

Infant acute lymphoblastic leukemia (ALL) is a rare disease and comprises about 4% of childhood ALL. Whereas the outcome of older children improved to >85% EFS, newly diagnosed infants (< 1 year of age) with ALL have a worse prognosis with an EFS of 47%. Especially those with mixed lineage leukemia- rearrangement (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%. Therefore upfront treatment need to be improved and these patients need innovative strategies directed 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. Also, clinical studies show that blinatumomab is an efficacious and well-tolerated treatment in children and adults with B-lineage ALL after intensive chemotherapy. We hypothesize that 1 course of blinatumomab can be added safely to the Interfant-06 backbone and will reduce MRD levels in infant ALL.
This pilot study will be performed in selected centers with experience in blinatumomab trials within the Interfant group (The Interfant study group is a collaborative group that consists of

all major European study groups and several large pediatric study groups outside Europe) and will be used to test the feasibility of adding blinatumomab to the Interfant-06 protocol. The toxicity and safety data of this pilot study will directly influence the drug choice and schedule given to infants in the worldwide collaborative COG/JPLSG/Interfant group trial.

Study objective

Blinatumomab may represent an additional therapeutic option for patients with infant ALL, who have an unmet need for treatment options that improve efficacy and/or have improved safety profile. The expected benefit will be improved efficacy of treatment. Blinatumomab will be added to the Interfant-06 protocol, and this might add additional toxicity. However less patients may need a haematopoetic stem cell transplantation because of reduction in MRD, decreasing the toxicity and treatment related mortality in this cohort of patients. Infants will be treated with blinatumomab after induction therapy, so not when having overt leukemia. They are therefore expected to experience less side effects than patients treated with blinatumomab for overt leukemia.

Study design

FPI: July 2018
LPI : July 2021
LPO: February 2022 (toxicity/feasibility/activity endpoints)
LPO: February 2024 (efficacy –EFS/OS)

Intervention

Blinatumomab is added to the standard arm of the Interfant-06 backbone (IA-IB-MARMA-OCTADAD-maintenance). After induction therapy (IA) patients will receive 1 course of blinatumomab 15 ìg/m2/day as a 4 week continuous infusion before protocol IB.

Contacts

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Eligibility criteria

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following 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 Interfant-06 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

A potential patient who meets any of the following criteria will be excluded from participation in this study:
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)
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 type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-07-2018
Enrollment:	30
Type:	Actual

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion
Date: 30-05-2017
Application type: First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 49535
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL5993
NTR-old	NTR6359
EU-CTR	EU-CTR2016-004674-17-NL
CCMO	NL59901.078.17
OMON	NL-OMON49535

Study results