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

EudraCT number: 2016-004674-17

Interfant network

Dutch Childhood Oncology Group
Early Clinical Trial Consortium
DCOG - ECTC

Princess máxima center
pediatric oncology

PROTOCOL TITLE

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Central laboratory for pharmacokinetic assessments	Wuxi, China PK samples to be send to the DCOG (see procedure manual)
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SUMMARY

Rationale: 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 needs 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.

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 of adding 1 course of blinatumomab to the Interfant-06 backbone
- to define the preliminary response rate of this regimen
- to assess pharmacokinetics of blinatumomab in infants

Study design: Prospective, single-arm, international multi-center study.

Study population: Newly diagnosed infants with ALL, who are treated according to the Interfant-06 protocol, stratified into the medium or high risk group, and have M1 or M2 marrow at the end of induction.

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 $\mu g/m^2$/day as a 4 week continuous infusion before protocol IB.

Endpoints:

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 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 $\geq$ 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)

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Whereas the outcome of older children with ALL improved to >85% EFS, infants with ALL have an EFS of less than 50%. Changes in treatment with chemotherapy did not significantly improve the outcome of infant ALL. These patients need innovative strategies directed against novel targets.

Blinatumomab has demonstrated activity in the treatment of adult and pediatric patients with ALL and is approved for the treatment of Philadelphia chromosome negative relapsed or refractory precursor B-ALL in adults and children (older than 28 days). Blinatumomab has been shown to have a manageable safety profile in adult and pediatric ALL. The majority of the (S)AEs is observed in the first week of treatment, during this time the most intensive monitoring is required. Medically important toxicities are neurological adverse events, but these appear not to be dose limiting in pediatric ALL, cytokine release syndrome (CRS), especially in children with relapsed/refractory ALL when used as induction treatment for overt leukemia and immune suppression, caused by decreased immunoglobulins and decreased neutrophils. The decreased immunoglobulins can be supplemented with intravenous immunoglobulins.

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.

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Due to contractual obligations with the international sponsor we are unable to provide the full protocol document.

More information about the trial can be found on the Australian New Zealand Clinical Trials Registry (anzctr.org.au) under record number ACTRN12620000542998.

Please contact the office of the Australian and New Zealand Children's Haematology / Oncology Group (ANZCHOG) for further details. Email: info@anzchog.org

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