A phase I/II study of Inotuzumab Ozogamicin as a single agent and in combination with chemotherapy for pediatric CD22-positive relapsed/refractory Acute Lymphoblastic Leukemia
Study ITCC-059

Published: 28-04-2016
Last updated: 07-09-2024

This study has been transitioned to CTIS with ID 2023-504694-20-00 check the CTIS register for the current data. - The primary objective of the Stratum 1A cohort is to establish the maximum tolerated dose of single agent InO when administered in...

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

Summary

ID

NL-OMON47372

Source
ToetsingOnline

Brief title
Inotuzumab ozogamicine for ALL

Condition

- Leukaemias

Synonym
bone marrow and lymph node cancer, leukemia and NHL

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: acute lymphoblastic leukemia, children, inotuzumab ozogamicin

Outcome measures

Primary outcome

- Primary endpoints for patients enrolled in Stratum 1A: Dose-limiting

toxicities (DLTs) during the first course of therapy.

- Primary endpoints for patients enrolled in Phase 2 cohort: Overall Response

Rate (ORR), defined as CR, CRi, CRp, measured as best response during InO

treatment.

- Primary endpoint for patients enrolled in Stratum 2: Safety and tolerability

Secondary outcome

Secondary endpoints for patients enrolled in Stratum 1A

1. Safety and tolerability:

2. Measures of anti-leukemic activity (Overall Response Rate after course 1,

best response over multiple courses, MRD levels, duration of response, % of

transplants after InO therapy, event free survival, overall survival).

3. Serum pharmacokinetic parameters of InO and unconjugated calicheamicin.

4. Pharmacodynamic parameters (relationship between response, CD22 expression /

CD22 saturation / calicheamicin sensitivity / Clonal evolution)

5. Other endpoints: Percentage of patients who exhibit ADA and the percentage

of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells or immunoglobulins following 4 weeks, 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT.

Secondary endpoints for patients enrolled in Phase 2 cohort

1. Safety:

2. Other measures of anti-leukemic activity: Overall Response Rate (ORR) after course 1, MRD Levels, Duration of response % of transplants, Event free survival (EFS), relapse, death of any cause and second malignancies, survival.

3. Serum pharmacokinetic parameters of InO and unconjugated calicheamicin.

4. Pharmacodynamic parameters: (relationship between response, CD22 expression / CD22 saturation / calicheamicin sensitivity / Clonal evolution

5. Other endpoints: Percentage of patients who exhibit ADA and the percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells or immunoglobulins following 4 weeks, 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT.

Secondary endpoints for patients enrolled in Stratum 2

1. Measures of anti-tumor activity (Overall remission rate (CR and PR) both after course 1 as well as overall best response in patients receiving multiple courses of InO therapy; Duration of response; % of transplants: EFS; relapse, death of any cause and second malignancies; Overall survival.

2. Serum pharmacokinetic parameters of InO and unconjugated calicheamicin.

3. Other endpoints: Percentage of patients who exhibit ADA and the percentage of patients responding to InO (ORR) without adequate recovery of CD19-positive B-cells or immunoglobulins following 4 weeks, 10 weeks, 3, 6 and 12 months after treatment with InO, excluding patients who have been transplanted from the date of HSCT.

Study description

Background summary

The prognosis for children with Acute Lymphoblastic Leukemia who experience a relapse or who are refractory to front-line therapy (about 20%) remains poor. Relapse is the main cause of treatment failure and death for these patients. Inotuzumab ozogamicin (InO) is an antibody-drug conjugate that binds with high affinity to CD22. It consists of the humanized IgG4 antibody linked to the cytotoxic agent calicheamicin. InO binds with high affinity to CD22. Upon binding to CD22 on target tumor cells, the antibody-antigen complex is rapidly internalized which subsequently leads to calicheamicin activation. Activation of calicheamicin causes DNA damage which often results in apoptosis and cell death.
CD22 is highly expressed in more than 90% cases of childhood B-precursor ALL. InO has been studied as a single agent for adult patients with B-cell ALL. Given the activity of InO in adult ALL and the medical need in pediatric relapsed/refractory ALL, development of InO in pediatric ALL seems highly warranted. This protocol is part of a Pediatric Investigational Plan (PIP), approved by the European Medicines Agency (EMEA) and Food and Drug Administration (FDA).

Study objective

This study has been transitioned to CTIS with ID 2023-504694-20-00 check the CTIS register for the current data.

- The primary objective of the Stratum 1A cohort is to establish the maximum tolerated dose of single agent InO when administered in children with CD22-positive relapsed/refractory BCPALL.
- The primary objective of the phase 2 cohort is to establish the activity (ORR) of single agent InO when administered in children with CD22-positive

relapsed/refractory BCP-ALL.
- The primary objective of stratum 2 is to explore the safety and tolerability of InO as a single agent in children with relapsed/refractory other CD22 positive B-cell malignancies.

Study design

Single-arm intervention study with medicinal product; using increasing dose-levels of InO (starting at a dosage of 80% of the adult RP2D).

Intervention

Patients are treated for up to 6 courses with Inotuzumab Ozogamicin. The first course lasts 22 days, subsequent courses last 28 days.
In each course 3 gifts of Ino are given (on day 1, day 8 and day 15). InO is given intravenously in a 1 hour infusion.

Study burden and risks

The patient burden is considered to be acceptable since the treatment would otherwise be commenced with another (off-label) medication, with the same response parameters and planned assessment procedures, perhaps less frequent though. Blood sampling and bone marrow sampling for scientific research will be combined where possible with samples / sample moments that are required for standard care, in order to keep the burden limited as much as possible.

The associated risk with participation is mainly due to (possibly unknown) adverse events of InO in this population, because the available toxicity information is based from studies with mainly adult patients.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015 CN
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015 CN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Age:
Patients must be >= 1 and < 18 years of age at the time of enrollment.
•The first 3 BCP-ALL patients on dose level 1 must be aged 6-18 yrs.
•Then at least 2 additional patients must be enrolled from age 1-6 yrs at the same dose level.
•After this: subsequent dose levels may enroll patients aged 1-18 yrs.
•In case 2 younger patients are not yet recruited, patients aged 6-18yrs may continue to be enrolled at dose level 1 until a maximum of 6 patients are enrolled. ;Stratum 1A: Diagnosis
First relapse of BCP-ALL post allogeneic HSCT or second or greater relapsed or refractory BCP-ALL, or refractory disease and must meet the following criteria:
•M2 or M3 marrow status (>= 5% blasts by morphology)
•CD22 surface antigen positive (either BM or PB)
•The first 6 patients must have M3 marrow status (>= 25% blasts by morphology).
•Refractory is defined as newly diagnosed patients who are induction failures after at least 2 previous regimens without attainment of remission, or patients with refractory first relapse after 1 previous reinduction regimen without attainment of remission. ;Phase 2 Cohort: Diagnosis
• First relapse of BCP-ALL post allogeneic HSCT or second or greater relapsed or refractory BCP-ALL, or refractory disease, and must meet the following criteria:
•M2 or M3 marrow status (>= 5% blasts by morphology)
•CD22 surface antigen positive (either BM or PB)
•Refractory is defined as newly diagnosed patients who are induction failures after at least 2 previous regimens without attainment of remission, or patients with refractory first relapse after 1 previous reinduction regimen without attainment of remission. ;Stratum 2: Diagnosis
Patients must have second or greater relapsed or refractory CD22-positive B-cell malignancy including but not limited to diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), Burkitt lymphoma, Burkitt leukemia or B-cell precursor lymphoblastic lymphoma:

• histologic verification of disease at original diagnosis or subsequent relapse.
•Patient must have evaluable or measurable disease documented by radiographic criteria or bone marrow disease present at study entry.
• CD22 surface antigen positive (in either biopsy material, BM or PB) ;Performance Level and Life Expectancy:
•Karnofsky > 60% for patients > 16 years of age and Lansky > 60% for patients <= 16 years of age.
•life expectancy of at least 6 weeks.;Prior Therapy:
Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy defined as resolution of all such non-hematologic toxicities to <= Grade 2 per the CTCAE 4.03.
•Chemotherapy: At least 7 days wash-out; except for hydroxyurea, 6-mp and steroids (wash-out 48 hrs) and intrathecal therapy (no wash-out). Patients who relapse while receiving maintenance chemotherapy will not be required to have a waiting period.
•Radiotherapy: At least 28 days must have elapsed since any prior radiation therapy.
•Hematopoietic Stem Cell Transplant: At least 90 days must have elapsed since previous allo-HSCT. No evidence of active GVHD; not receiving GVHD prophylaxis or treatment.
•Hematopoietic growth factors: At least 7 days wash-out of therapy with GCSF or other growth factors. At least 14 days wash-out of pegfilgrastim (Neulasta®).
•Immunotherapy: At least 42 days wash-out of any type of immunotherapy, e.g. CART therapy. No prior CD22-targeted therapy or anti-tumor vaccines permitted.
•Monoclonal antibodies: wash-out of at least 3 half-lives of the antibody (ie: Rituximab = 66 days, Epratuzumab = 69 days), with the exclusion of blinatumomab. Patients must have been off blinatumomab infusion for at least 14 days and all drug-related toxicity must have resolved to grade 2 or lower.
•Investigational drugs: At least 7 days or 5 drug half-lives (whichever is longer) must have elapsed since prior treatment with any experimental drug (with the exception of monoclonal antibodies).
•no prior treatment with a calicheamicin-conjugated antibody (e.g. gemtuzumab ozogamicin).
Renal and Hepatic Function:
•serum creatinine <= 1.5 x ULN according to age. If the serum creatinine is > than 1.5 xULN, the patient must have a radioisotope GFR >= 70mL/min/1.73m2.
•AST and ALT <= 2.5 x ULN.
•total bilirubin <= 1.5 x ULN (unless patient has documented Gilbert syndrome &AST and ALT are <=2.5 x ULN).
Cardiac Function:
•shortening fraction >= 30% by ECG or an ejection fraction > 50% by MUGA.
Reproductive Function:
•If applicable, negative urine or serum pregnancy test confirmed prior to enrollment.
•If applicable, agree not to breastfeed while on this study.
•If applicable, agree using effective method of contraception during the study and for 5 months (for male patients) or 8 months (for female patients) after the last dose of InO.

Exclusion criteria

Isolated extramedullary relapse:
•Patients with isolated extramedullary disease are excluded (not applicable to lymphoma patients except for isolated CNS-relapse);VOD/SOS:
•Patients with any history of prior or ongoing VOD/SOS per the modified Seattle criteria are excluded, as specified in appendix 3, or prior liver-failure [defined as severe acute liver injury with encephalopathy and impaired synthetic function (INR of >=1.5)]. ;Infection:
Patients will be excluded if they have a systemic fungal, bacterial, viral or other infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient may not have:
•A requirement for vasopressors;
•Positive blood culture within 48 hours of study enrollment;
•Fever above 38.2 within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability.
•A positive fungal culture within 30 days of study enrollment.
•Active fungal, viral, bacterial, or protozoal infection requiring IV or oral treatment. Chronic prophylaxis therapy to prevent infections is allowed.

Other anti-cancer therapy:
•Patients will be excluded if there is a plan to administer non-protocol anti-cancer therapy including but not limited to chemotherapy, radiation therapy, or immunotherapy during the study period. ;Allergic reaction:
•Patients with prior Grade 3/4 allergic reaction to a monoclonal antibody are excluded.;Concurrent disease:
•Patients will be excluded if they have significant concurrent disease, illness, psychiatric disorder or social issue that would compromise patient safety or compliance with protocol therapy, interfere with consent, study participation, follow up, or interpretation of study results.
•Children with Down syndrome are excluded from participation in the dose finding part (stratum 1A), but not in the stratum 1 phase 2 cohort.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-01-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BESPONSA
Generic name:	inotuzumab ozogamicin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-04-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2018
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-09-2022
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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-504694-20-00
EudraCT	EUCTR2016-000227-71-NL
CCMO	NL56327.078.16