Comparative efficacy and safety of two asparaginase preparations in children with previously untreated acute lymphoblastic leukemia (ALL), a phase III clinical trial

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This multicentre phase III study is designed to assess the efficacy and safety of recombinant versus E-Coli derived Aaparaginase from Medac, during treatment of children with newly diagnosed ALL according to the DCOG ALL-10 protocol.Futhermore: To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON33823

Source
ToetsingOnline

Brief title
MC-ASP.5/ALL

Condition

- Leukaemias

Synonym
acute lymphoblastic leukemia in children

Research involving
Human

Sponsors and support

Primary sponsor: Medac
Source(s) of monetary or material Support: door de sponsor Medac

Intervention

Keyword: acute lymphoblastic leukemia, children, E-coli asparaginase, recombinant asparaginase

Outcome measures

Primary outcome

To determine the rate of patients with complete asparagine depletion in serum during induction treatment; to demonstrate non-inferiority of recombinant versus E-Coli derived Asparaginase Medac.

Secondary outcome

ASN depletion in CSF will be measured as a secondary endpoint at day 33 of induction treatment.

A futher surrogate parameter for treatment efficacy of an ASnase preparation are trough levels of ASNase activity in serum just before the next ASNase infusion.

As an addition pharmacokenetic parameter, ASNase activity levels in CSF during induction treatment phase A will be measured.

Besides ASN, concentrations of amino acid aspartic acid (ASP), glutamine (GLN), and glutamic acid (GLU) will be measured in serum CSF at defined timepoints during induction treatment. In high risk patients ASN-levels will be additionally measured at defined time-points during post-induction treatment.

Trough levels of ASNase activity and ASN, ASP, GLN and GLU-levels in serum will be measured at defined timepoints during post-induction treatment.

Furthermore, the number of patients in each risk group who could complete their full course of ASNase treatment as scheduled will be documented, and assess of incidence of AE's and the incidence of patients with hypersensitivity reactions to the first post-induction dose.

As another secondary endpoint, efficacy of the treatment will be evaluated wtihin this study by measuring the CR rate and the MRD status after induction treatment phase A (day 33 or thereafter)

Complete remission (CR) is defined on morphological grounds by the presence of < 5% leukemic blasts in bone marrow (M1 marrow), no leukemic blasts in peripheral blood and CSF, no other documented extramedullary leukemia with the exeption of testicular enlargement, and regeneraring haematopoieses.

In addition, the secondary endpoints relapse rate and event-free survival (EFS) will be evaluated at the end of the study. Events are relapse or death.

Study description

Background summary

Acute lymphoblastic leukemia (ALL) is a clonal disease resulting from genetic mutations and transformations of a single early progenitor lymphoid cell. Uncontrolled expansion of leukemis blasts in the bone marrow leads to suppression of normal haematopoiesis as well as disseminated infiltration of organs and release of blasts into the perpheral blood.

ALL is the most common malignancy in children, accounting for 30% of all cancers and 80% of all leukemias in this age group.

The treatment of ALL depends on the use of intensive multi-agent chemotherapy given for 2 years. In selected patients irradiation and/or stem cell transplantation are used. Patients with ALL are usually treated within a study protocol. In the Netherlands, children with newly diagnosed ALL are currently treated with the national protocol of the Dutch Childhood Oncology Group (DCOG)

ALL 10.

Asparaginase (ASNase) is an essential component of treatment of children with newly diagnosed ALL. Several recently published trials have clearly demonstrated that this drug contributes to the total treatment outcome of children with ALL by at least 10 - 20%. Hence, allergy against asparaginase is an important clinical problem, as this may lead to early interruption of asparaginase therapy, resulting in a lower cumulative asparaginase dose which worsens prognosis.

Recombinant ASNase (rASNase) has similar enzymatic, pharmacokinetic and pharmacodynamic properties as E.coli-ASNase but is a much purer preparation. This new ASNase may therefore cause less hypersensitivity reactions than the currently approved drugs. In a recent pilot study at Erasmus MC it was shown that this drug has a similar safety profile as regular E-Coli derived asparaginase, and leads to similar asparagine depletion. The current study is intended to compare the efficacy of the new rASNase preparation versus the commercially available E-Coli derived Asparaginase from Medac in a larger number of children with newly diagnosed ALL.

Study objective

This multicentre phase III study is designed to assess the efficacy and safety of recombinant versus E-Coli derived Aaparaginase from Medac, during treatment of children with newly diagnosed ALL according to the DCOG ALL-10 protocol.

Futhermore: To determine the rate of patients with complete asparagine depletion in serum during induction treatment, and to demonstrate non-inferiority of rASNase compared to E-Coli derived Asparaginase Medac.

Study design

This is a multicentre, randomised, active-controlled, double-blind, parallel-group phase III clinical trial to evaluate the efficacy and safety of repeated ASNase infusions (recombinant versus E-Coli derived Asparaginase Medac)

Intervention

Treatment consists of either recombinant asparaginase - or E-Coli derived Asparaginase Medac infusions (8 doses) in teh induction part of teh protocol.

For post-induction treatment, all patients are stratified into 3 risk groups (standard risk, medium risk and high risk) based on stratification criteria defined in the ALL 10 protocol. Patients will receive different treatment according to their risk group assignment.

For patients in the SR and MR groups treatmnet will be continued using PEG-asparaginase, and they will be followed for allergic reactions. In addition, limited blood sampling will be performed to detect antibodies and check asparaginase levels.

Patients in the HR-group will continue treatment with the standard E-Coli derived asparaginase in their chemotherapy blocks 1,2 4 and 5, and the so-called protocol II. Therefore they will continue with the study and recieve either recombinant or E-Coli asparaginse. Each patient will receive the same product as in induction.

Study burden and risks

The risks and burden of participation are similar to a standard treatment for pediatric ALL. A potential benefit may arise if we can prove that patients with recombinant asparaginse indeed have fewer allergic reactions to asparagine, which may increase the cumulative asparaginase dose and lead to a better prognosis for these children. Potential risks are associated with the blood and CSF sampling - although this will be combined with regular blood and CSF sampling time points according to the ALL-10 protocol. New side-effects may occur in teh recombinant asparaginase group, as only limited experience exists in humans with this compound, althuogh this is unlikely base don the chemical, Pk and PD properties of the drug.

Contacts

Public
Medac

Theaterstr. 6
D-22880 Wedel
DE
Scientific
Medac

Theaterstr. 6
D-22880 Wedel
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Previously untreated T-lineage or percusor B-lineage ALL
Morphological proof of ALL (diagnose established by bone marrow morphology with greater than or equal to 25% blasts)
Age between 1 year and 19 years
Treatment according to DCOG ALL 10 protocol
Written informed consent

Exclusion criteria

Mature B-lineage ALL
Patients with secondary ALL
Known allergy to any ASNase preparation
General health status according to Karnofsky/Lansky score < 40%
Pre-existing known coalgulopathy (e.e. haemophilia)
Pre-existing pancreatitis
Liver insufficiency (bili >50 umol/l, ALAT/ASAT >10xULN)
Other current malignancies
Pregnacy, breast feeding

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-10-2008
Enrollment:	198
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Asparaginase medac
Generic name:	Asparaginase medac
Product type:	Medicine
Brand name:	rASNase
Generic name:	recombinant Asparaginase

Ethics review

Approved WMO Date:	11-04-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2009
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-10-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-09-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2011
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
EudraCT	EUCTR2006-003180-31-NL
CCMO	NL21435.078.08