Protocol ALL-11: Treatment study protocol for ALL in the Netherlands

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

Summary

ID

NL-OMON29675

Source
NTR

Brief title
ALL11

Condition

- Leukaemias

Health condition

Acute lymfatische leukemie bij kinderen acute lymphoblastic leukemia in children

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor kinderoncologie
Source(s) of monetary or material Support: Dutch Childhood Ongology Group

Intervention

Explanation

Outcome measures

Primary outcome
1. Primary endpoints are survival, EFS, CIR, death in induction, death in remission and toxicity.

2. Primary endpoint is the number of allergic reactions/silent inactivation; secondary endpoints are toxicity, EFS and survival.

3. Primary endpoint is the number of admissions for fever and the number of courses with therapeutic antibiotics in both groups.

4. Primary endpoint is the number of patients with allergic reaction or silent inactivation to PEGasparaginase and who are therefore switched to Erwinase. Secondary endpoints are the average cumulative dose of PEGasparaginase administered to patients in the MR arm A compared to the historical control of the ALL-10 MR study.

Study description

Background summary
Treatment study protocol of the Dutch Childhood Oncology Group for children and adolescents (1-19 year) with newly diagnosed acute lymphoblastic leukemia.

Since 1999, infants with ALL diagnosed <1 year of age are treated on specific protocols of the Interfant collaborative group. Patients with the Philadelphia chromosome positive ALL chromosomes are treated on specific protocols of the EsPhALL group since 2004. All other ALL patients were treated according to the ALL-10 protocol that started in 2004. This treatment protocol included 3 different stratification arms (standard risk, medium risk and high risk) which are very different in their intensity. The factors used for risk group stratification in the ALL-10 protocol were the presence of t[4;11], a poor response to initial therapy, as measured in the peripheral

blood by response to prednisone and one intrathecal dose of methotrexate (MTX) after one week of therapy (so-called prednisone response), induction failure after 33 days of combination chemotherapy and the minimal residual disease measured by PCR at day 33 and day 79. The ALL-10 protocol was the first DCOG protocol where therapy stratification was done by analysis of MRD. MRD was used for this purpose because an earlier study showed that MRD had a very strong prognostic value: patients with very low levels of MRD (standard

risk group) had an excellent outcome, patients with high levels of MRD (high risk group) a poor outcome and patients with intermediate levels (medium risk group) had an intermediate outcome.

The ALL-10 protocol is - based upon its very good outcome - used as basis for the ALL-11 protocol.

Study objective

1. To improve the overall outcome as compared to the previous protocols of the DCOG, especially ALL-9 and ALL-10. This is aimed for by decreasing therapy for part of the patients (TEL/AML1, Down syndrome, PPR only), increasing therapy for IKZF1 mutated cases, decreasing the cumulative dose of anthracyclines, omitting cranial irradiation and total body irradiation and individualizing asparaginase therapy for all patients.

2. Does a continuous schedule of Asparaginase lead to less allergic reaction/inactivation of Asparaginase than the standard non continuous schedule of Asparaginase? Patients are randomized to receive noncontinuous PEGasparaginase in IA (induction) and intensification of the Medium Risk group (standard arm A) or to receive continuous PEGasparaginase in IA, IB, M and intensification, (continuous arm B) with the same cumulative number of doses of PEGasparaginase.

3. Does prophylactic administration of intravenous immunoglobulins reduce the number of infections during the intensive treatment phases? Patients are randomized in the induction and MR treatment group to receive or not receive prophylactic immunoglobulins

4. Individualize the dose schedule of asparaginase by therapeutic drug monitoring in order to detect silent inactivation of asparaginase, to prevent allergic/anaphylactic reactions, to switch Asparaginase preparation in time and to prevent too high levels with possible toxicity.

Study design

National multicenter open-label randomized clinical trial (Phase III)

1) Stratificatie into risk groups, based upon riskfactors

Standard risk (SR) group:

• MRD-negativity at TP1 (day 33) and at TP2 (day 79 before start of Protocol M) AND

• no CNS involvement or testis involvement at diagnosis AND

• no prednisone poor response at day 8 AND

• absence of any HR criterion

Medium risk (MR) group

• inconclusive/missing MRD results or MRD-positivity at TP1 (day 33) and/or at TP2 (day 79 before the start of protocol M), but MRD level at day 79 < 10–3 AND

• absence of any HR criterion

High Risk (HR) group:

• MRD level > 10-3 or unknown at TP1 and MRD level of ≥ 10–3 at TP2, OR

• presence of the t(4;11)(q11;q23) translocation or the corresponding fusion gene MLL/AF4, OR

• no complete remission at day 33

• Note: children with Down syndrome that fulfill the HR criteria are assigned to the MR group

2) Randomisations:

A. Does a continuous schedule of Asparaginase lead to less allergic reaction/inactivation of Asparaginase than the standard non continuous schedule of Asparaginase? Patients are randomized to receive noncontinuous PEGasparaginase in IA (induction) and intensification of the Medium Risk group (standard arm A) or to receive continuous PEGasparaginase in IA, IB, M and intensification, (continuous arm B) with the same cumulative number of doses of PEGasparaginase.

B. Does prophylactic administration of intravenous immunoglobulins reduce the number of infections during the intensive treatment phases? Patients are randomized in the induction and MR treatment group to receive or not receive prophylactic immunoglobulins

Intervention
IVIG (Nanogam)

PEG-L-asparaginase (Oncospar)

Study burden and risks
Patients may suffer from additional burden and risk due to the IVIg administrations. However, this study aims at reducing the risk of serious infections, and therefore we feel that the additional burden and risks may be justified.

Contacts

Public
Prinses Máxima Centrum voor kinderoncologie

Prof. dr. R. Pieters
Heidelberglaan 25
3584 CS
Utrecht
The Netherlands

The Netherlands
088-972 72 72
Scientific
Prinses Máxima Centrum voor kinderoncologie

Prof. dr. R. Pieters
Heidelberglaan 25
3584 CS
Utrecht
The Netherlands

The Netherlands
088-972 72 72

Eligibility criteria

Age
Babies and toddlers (28 days-23 months)
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Children (2-11 years)
Children (2-11 years)
Adolescents (12-15 years)
Adolescents (12-15 years)
Adolescents (16-17 years)

Adolescents (16-17 years)

Inclusion criteria

1. Newly diagnosed patients with T-lineage or precursor-B lineage ALL (patients with mature B-ALL are not eligible)

2. Age between > 1 and < 19 years

3. Informed consent signed by parents/guardians and patient if 12 years or older

4. Diagnosis ALL confirmed by DCOG laboratory

5. Patient should be treated in a Dutch Childhood Oncology Centre

6. Patient should be >3 months settled in The Netherlands at diagnosis

Exclusion criteria

1. Age ≥ 19 years at diagnosis

2. Age < 366 days at diagnosis (infant ALL); these patients are eligible for the Interfant protocol

3. Patients with secondary ALL

4. Patients with mature B-ALL (immunophenotypical or documented presence of karyotype t(8;14), t(2;8), t(8;22) and breakpoint as in B-ALL)

5. Patients with relapsed ALL

6. Pre-existing contra-indications for treatment according to (parts of) protocol ALL-11.

7. Essential data missing (in consultation with the protocol chairman)

8. Treatment with systemic corticosteroids and/or cytostatics in a 4-week interval prior to diagnosis. One exception is the use of corticosteroids as emergency treatment.

9. Patients with Ph-positive ALL (documented presence of t(9;22)(q34;q11) and/or of the BCR/ABL fusion transcript). These patients will be transferred to the EsPhALL protocol in induction according to the guidelines of the EsPhALL protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2012
Enrollment:	630
Type:	Actual

IPD sharing statement

Plan to share IPD: No

Ethics review

Approved WMO

Date:	19-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

ID: 47149
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL3227
NTR-old	NTR3379
EudraCT	2012-000067-25
CCMO	NL39400.078.12
OMON	NL-OMON47149

Study results

Results posted: 07-12-2023

Actual enrolment: 819

Summary results
"The DCOG ALL11 showed that the five-year survival for children with acute lymphatic leukaemia increased to 94%. The ALL11 included 800 Dutch children and examined modified treatment protocols for four subgroups. The modifications were found to have a positive effect on survival and quality of life.

The effect of modified treatment in specific groups of children with leukaemia, including those with a so-called Ikaros abnormality (IFZF1del), was examined. In this study, these children received an extra year of chemotherapy in the 'maintenance phase' on top of the first two years of treatment. This modification led to a nearly three times lower risk of cancer recurrence: it only happened in 9% of them, compared to 26% of children in the previous treatment protocol.

In the ALL-11 protocol, doctors and researchers also looked at the effect of less intensive treatment for three other groups of children. These included children with a DNA abnormality in their leukaemia cells that is associated with a very high cure rate (ETV6::RUNX1), and children with Down's syndrome who suffer a lot of side effects from therapy. These children were given a lower amount of anthracyclines, a particular type of chemotherapy that increases the risk of heart damage and infections. The modification proved to be a good choice: the children had the same or even better survival rate while their quality of life improved due to a lower risk of infections and less risk of heart damage."

Baseline characteristics
Patients with ALL, 1-19 years old

First publication

17-07-2023