Protocol ALL-11:Treatment study protocol of the Dutch Childhood Oncology Group for children and adolescents (1-19 year) with newly diagnosed acute lymphoblastic leukemia

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

Summary

ID

NL-OMON47149

Source
ToetsingOnline

Brief title
DCOG Protocol ALL-11

Condition

- Leukaemias
- Hepatobiliary neoplasms malignant and unspecified

Synonym
cancer from the bone marrow, Leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Kinderoncologie Nederland
Source(s) of monetary or material Support: Ministerie van OC&W,bedrijven;stichting Go4Children en KIKA fonds,Sanquin (leveren IvIg als studiemediatie)

Intervention

Keyword: adolescents, ALL, children, treatment

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 infectious episodes for which patients are admitted to the hospital and receive therapeutic antibiotics or antifungals.

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.

Secondary outcome

Not applicable.

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 outome - 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

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.

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 an drisks may be justified.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

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:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2012
Enrollment:	770
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nanogam 50 mg/ml, solution for intravenous infusion
Generic name:	Human Immunoglobulines
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Oncaspar
Generic name:	PEG-L-asparaginase

Ethics review

Approved WMO Date:	13-07-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-10-2012

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-11-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-10-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-09-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	23-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-03-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-11-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-03-2020
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2021
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

ID: 29675
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-000067-25-NL
CCMO	NL39400.078.12
OMON	NL-OMON29675