ALLTogether1- A Treatment study protocol of the ALLTogether Consortium for children and young adults (0-45 years of age) with newly diagnosed acute lymphoblastic leukaemia (ALL)

Published: 16-12-2019
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This study has been transitioned to CTIS with ID 2022-501050-11-01 check the CTIS register for the current data. The primary objective of ALLTogether is to improve survival and quality of survival in children and young adults with acute...

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

Summary

ID

NL-OMON55098

Source
ToetsingOnline

Brief title
ALLTogether1

Condition

- Leukaemias

Synonym
acute lymphoblastic leukemia, blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: Karolinska University Hospital
Source(s) of monetary or material Support: Amgen,Inotuzumab Ozogamicin wordt door Pfizer gratis geleverd voor de studie; 6-Tioguanine wordt door Nova laboratories gratis geleverd voor de studie; Blinatumomab wordt door Amgen gratis geleverd voor de studie. Analyses nodig voor de Therapeutic Drug Monitoring van Asparaginase worden vergoed door Servier.,Nova laboratories,Pfizer,Servier

Intervention

Keyword: acute lymphoblastic leukemia, children

Outcome measures

Primary outcome

- The primary endpoint for the whole protocol (compared with the legacy

protocols of the participating study-groups forming the consortium) is

event-free survival (EFS) - as defined in the protocol.

- The primary endpoint for the randomised interventions is disease-free

survival (DFS) - as defined in the protocol.

- The primary endpoint for the DS study is fraction of MRD undetectable

patients (*Complete MRD response*) at the end of one cycle of Blinatumomab

Secondary outcome

Main study secondary end-points:

The most important secondary outcome is overall survival (OS).

Additional secondary measures of antileukaemic efficacy are: rate of -death

during induction, -resistant disease, cumulative incidence of: -relapse (ciR),

-death in first complete remission (ciDCR1) and -second malignancy (ciSMN).

Over- and under-treatment events will also be combined into resulting

treatment-related mortality (TRM) and leukaemia specific mortality (LSM) rates.
Since over-treatment also includes cured patients who suffer potentially permanent side-effects, data will be collected regarding the incidence of some adverse events of special interest.
De-escalation of therapy may also result in relapses that have to be rescued with allogeneic stem-cell transplant (allo-SCT), which is associated with serious permanent side effects. Therefore, the incidence of allo-HSCT in CR1 and CR2 will also be measured.
An important aspect of evaluation of the quality of survival is measurement of quality of life (QoL). The whole protocol, as well as each of the non-randomised and randomised interventions will also be evaluated by measurements of quality of life (QoL). QoL will be measured by EQ5D-based instruments before and after all the randomised phases in all randomisations as well as later in the therapy and after cessation of treatment.

R1 and R2 secondary end-points:

Efficacy:

• Overall survival (OS)

• The components of the primary end-point - DFS (ciR, ciDCR1 and ciSMN) are relevant secondary end-points since they are likely to work in opposite directions in a de-escalation setting

• Fraction of surviving patients treated with allogeneic stem-cell transplant

in second remission and cumulative incidence of HSCT in CR2 will also be measured

Toxicity:

The studies are powered to answer the primary end-point non-inferiority question with a certain safety-margin. Even if reduction of exposure to potentially toxic therapy is an objective in itself, it is also reasonable to show some immediately measurable benefit from the reduction of therapy if the study is successful and non-inferiority can be shown.

Non-lethal toxicities for the DI-phase (R1 and R2):

• Rate of febrile neutropenia (yes/no) and agent (if isolated from a sterile site/blood)

• Rate of invasive fungal infection (yes/no) together with assessment of "possible"/"probable"/"proven" and agent (if isolated from sterile site/blood/BAL)

• Rate of serious viral reactivation (EBV, VZV, HSV and CMV), mucositis with need for intravenous analgesics and/or nutritional support with parenteral nutrition

• The incidence of SAEs (except AESI)

• The time-interval between the start of DI and the start of the next treatment- phase in days.

• Rate of cardiac failure or serious arrhythmia (CTCAE >= grade 3)

In addition the following quantifiable measures of the toxicities listed above will be measured at the same time-points:

• days admitted to hospital during the randomised phase and until the start of the next treatment phase

• days on iv antibiotics

• days on advanced antifungals

• days on iv analgesics and/or nutritional support with parenteral nutrition

• Body-mass index at the time of cessation of therapy and 5 years after the end of therapy.

Non-lethal toxicity for the Maintenance-phase (R2) measured at the beginning of Maintenance and every 3 months during the maintenance-phase:

• Rate of VCR-neuropathy Grade >=3 according to the PdL definition

• The number of doses of VCR that had to be reduced or omitted

• Cumulative incidence of symptomatic osteonecrosis + grade.

Secondary end-points R3-InO

Efficacy:

• Overall survival (OS)

• Cumulative incidence of relapse (CIR)

• Occurrence of CD22 negative relapse

Toxicity:

• Incidence and severity of SOS/VOD all grades

• Incidence and severity of other liver toxicity (defined as AST/ALT elevations grade > 3 and bilirubin grade > 3)

• Incidence and severity of infections CTCAE grade > 3

• Incidence and duration of B-cell depletion reflected by immunoglobulin levels/IV immunoglobulin supplementation

Exploratory end-point:

CD22 expression level of leukemic cells in bone marrow samples at diagnosis and at TP2 (day 71).

Secondary end-points DS:

• Overall survival

• Incidence of relapse

• Incidence of Death in Complete Remission

• Incidence of second malignancies

• Incidence of CD19 negative relapse

• Event Free Survival

• Incidence of Blinatumomab refractory disease

• Incidence of Protocol Therapy Failure

Study description

Background summary

Acute Lymphoblastic Leukaemia (ALL) is the most common form of childhood malignancy, with an incidence that varies between approximately 100 children per year in the Netherlands. The incidence in adults is approximately a third of that in children, indicating that the disease is relatively much more common among children when the limited time-span of childhood is taken into account. Treatment results have improved over time due to risk-adapted therapy developed by cooperative groups.
In the discussions leading up to the formation of the consortium, representatives from the study-groups identified four major problem areas that should be addressed. The problem areas identified are:

1) The cure of the remaining <10% of children and 20-30% of adults that still die of ALL:
The prognosis for children and young adults with ALL has improved dramatically in the last 40-50 years. Currently, overall survival exceeds 90% for children and 70-80% for young adults. The identification of clinical and genetic risk-factors and increasingly sophisticated means of measuring early response to therapy by minimal residual disease (MRD) have refined the risk-stratification and improved risk-adapted treatment protocols. This intensification has had several effects apart from the generally improved outcome:
- truly resistant disease, not responding to any therapeutic measures has become very rare in ALL in children and young adults treated according to contemporary protocols;
- further general intensification of therapy is not likely to improve the outcome, since the reduction in relapses means that, despite best possible care, an increasing fraction of adverse events are the result of treatment-related causes - death in first complete remission (DCR1) and second malignant neoplasm (SMN)

2) Over-treatment:
When treatment-results are compared over a longer time-period, considered in the context of the therapy given at that time and the successive intensification of therapy generally, it is obvious that a substantial fraction of all patients are over-treated with contemporary treatment protocols.
The over-treatment has several serious consequences:
- one of the limiting factors for further intensification is the likely rise in treatment-related mortality, which is currently 3-5% of all paediatric patients, but higher for young adults; Treatment related mortality is particularly high in Down Syndrome with an incidence of between 10-20 %
- the consequences of acute and chronic toxicity is a fraction of longterm survivors that suffer from serious long-term consequences, which may limit their remaining expected life-span and impair their quality of life as a result of the therapy;
- the protracted standard therapy imposes unnecessary burdens on the patients and their families with consequences for schooling, work and social life.

3) The identification of new biological sub-groups with potential new targets for therapy.

4) Lacking statistical power with improving results

Study objective

This study has been transitioned to CTIS with ID 2022-501050-11-01 check the CTIS register for the current data.

The primary objective of ALLTogether is to improve survival and quality of survival in children and young adults with acute lymphoblastic leukaemia

Study design

The ALLTogether treatment protocol is an international multi-centre prospective, open label study with several (phase III) randomised parts. The backbone of the protocol is the basis of a platform onto which several randomisations and other interventions can be added

Intervention

- R1: omission of Doxorubicin in the delayed intensification phase of the SR treatment
- R2: omission of Doxorubicin in the delayed intensification phase or Vincristine-Dexamethasone pulses in maintenance phase of the IR-low treatment
- R3: addition of Inotuzumab Ozogamicin (InO) or 6-Tiolguanine to the maintenance phase of the IR-high treatment
- Addition of Imatinib to the treatment of patients with ABL-class fusion positive ALL; collection of additional bonemarrow and blood at standard sampling timepoints
- Replacement of 2 consolidation cycles with 2 cycles of Blinatumomab in IR/HR patients with Down Syndrome
- Quality of Life questionnaires
- Asparaginase peak levels study: additional blood sampling at standard sampling timepoints
- CSF-FLOW study: additional CSF fluid sampling at standard sampling timepoints
- MRD study: collection of additional Bonemarrow at the end of the Consolidation phase, at standard sampling timepoint
- Maintenance, TDM MTX/6MP: additional blood sampling during Maintenance every 1-3 months, at standard sampling timepoints.
- BRAIN study: play some computer games after end of treatment.

Study burden and risks

The ALLTogether1 treatment protocol is a developed by a consortium of study

groups from 14 different European countries. Treatment according to this protocol is the standard treatment for children and young adults with ALL in these European countries. In the Netherlands all patients until 18 years of age will be treated according to this protocol in the Princess Máxima Center. Young adults from 19 until 25 years of age will be treated according to this protocol in the UMC Utrecht.
Most important risks are standard in a (pediatric) oncology treatment. There are no additional risks for the extra blood/bonemarrow/CSF fluid samplings at the standard sampling timepoints. Extra bloodsamples are taken from the PAC at times that this is already in use for a standard blood sampling.
In R1 and R2 there is a potential additional risk due to deintensification of therapy.
In R3 the possible additional risks are mainly the side effects of inotuzumab ozogamicin or 6-tioguanin, including currently unknown side effects. See also the InO subprotocol (ch. 13-Structured Risk Analysis), and the TEAM subprotocol.
In the TKI study the possible additional risks are mainly the side effects of Imatinib.
In the DS study the possible additional risks are mainly the side effects of Blinatumomab.

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)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

1. Patients newly diagnosed with T-lymphoblastic (T-cell) or B-lymphoblastic precursor (BCP) leukaemia (ALL) according to the WHO-classification of Tumours of Haematopetic and Lymphoid Tissues (Revised 4th edition 2017) and with a diagnosis confirmed by an accredited laboratory at a participating paediatric oncology or adult haematology centre.
2. Age > 0 days and < 46 years (one day before 46th birthday) at the time of diagnosis.
3. Patients with surface IG negative BCP-ALL and an IG::MYC rearrangement unless they have a concurrent BCL2/6 rearrangement. T-ALL patients with MYC translocations.
4. Informed consent signed by the patient and/or parents/legal guardians according to country-specific age-related guidelines.
5. The ALL diagnosis should be confirmed by an accredited laboratory at a participating paediatric oncology or adult haematology centre.
6. The patient should be diagnosed and treated at a participating paediatric oncology or adult haematology centre in the participating countries.
7. The patient should be a resident in one of the participating countries on a permanent basis or should intend to settle in a participating country, for instance by an application for asylum. Patients who are visiting the country as tourists should not be included. However, returning expatriots with primary diagnosis abroad may be included if no treatment has been administered and the diagnostic procedures are repeated at a participating centre.
8. All women of childbearing potential (WOCBP) have to have a negative pregnancy test within 2 weeks prior to the start of treatment.

For each intervention/randomisation an additional set of inclusion-criteria is provided.

Exclusion criteria

1. Age < 365 days at diagnosis and KMT2A-rearranged (KMT2A-r) BCP ALL

(documented presence of a KMT2A-split by FISH and/or a KMT2A transcript). These patients will be transfered to an appropriate trial for KMT2A-r BCP infant ALL if available.
2. Age > 45 years at diagnosis (from the 46th birthday onwards).
3. Patients with a previous malignant diagnosis (ALL as a second malignant neoplasm - SMN).
4. Relapse of ALL.
5. Patients with mature B-ALL (as defined by Surface Ig positivity or documented presence of one of the t(8;14)(q24;q32), t(2;8)(p12;q24), t(8;22)(q24;q11) translocations involving the MYC gene and breakpoint as in mature B-NHL/ALL) or any patients with IG::MYC and a concurrent BCL2/6 rearrangement.
6. Patients with Ph-positive ALL (documented presence of t(9;22)(q34;q11) and/or of the BCR::ABL1 fusion transcript). These patients will be transferred to an adequate trial for t(9;22) if available.
7. Previously known ALL prone syndromes (e.g. Li-Fraumeni syndrome, germline ETV6 mutation), except for Down syndrome. Exploration for such ALL prone syndromes is not mandatory and patients in whom genetic work-up reveals a new germline mutation (index-cases) will remain in the study.
8. Treatment with systemic corticosteroids (>10mg/m2/day) for more than one week and/or other chemotherapeutic agents in a 4-week interval prior to diagnosis (pre-treatment).
9. Pre-existing contraindications to any treatment according to the ALLTogether protocol (constitutional or acquired disease prior to the diagnosis of ALL preventing adequate treatment).
10. Any other disease or condition, as determined by the investigator, which could interfere with the participation in the study according to the study protocol, or with the ability of the patients to cooperate and comply with the study procedures.
11. Women of childbearing potential who are pregnant at the time of diagnosis.
12. Women of childbearing potential and fertile men who are sexually active and are unwilling to use adequate contraception during therapy. Efficient birth control is required, see section 17.7.
13. Female patients, who are breast-feeding.
14. Essential data missing from the registration of characteristics at diagnosis (in consultation with the protocol chair).

For each intervention/randomisation an additional set of exclusion-criteria is provided.

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:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-07-2020
Enrollment:	565
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Besponsa
Generic name:	inotuzumab ozogamicin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Dexamethasone
Generic name:	Dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	methotrexate
Generic name:	methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Vincristin
Generic name:	Vincristin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-12-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-05-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-02-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-08-2023

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	03-01-2024
Application type:	Amendment
Review commission:	METC NedMec

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	CTIS2022-501050-11-01
EudraCT	EUCTR2018-001795-38-NL
ClinicalTrials.gov	NCT04307576
CCMO	NL71370.041.19