International phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones

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This study has been transitioned to CTIS with ID 2024-515499-12-00 check the CTIS register for the current data. The primary objective is reducing treatment-related morbidity and mortality without adversely impacting DFS in Ph+ ALL patients,...

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

Summary

ID

NL-OMON52698

Source
ToetsingOnline

Brief title
EsPhALL2017/COGAALL1631

Condition

- Leukaemias

Synonym
bloodcancer, leukemia

Research involving

Human

Sponsors and support

Primary sponsor: Università di Milano - Bicocca
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: adolescents, ALL, children, Philadelphia chromosome

Outcome measures

Primary outcome

To compare disease-free survival (DFS) of Standard Risk (SR) pediatric Ph+ ALL treated with continuous imatinib combined with either a high-risk COG ALL chemotherapy backbone or the more intensive EsPhALL chemotherapy backbone.

Secondary outcome

- To compare disease free survival (DFS) of SR pediatric Ph+ and ABL-class fusion positive ALL patients treated with continuous imatinib combined with either a high-risk COG-ALL chemotherapy backbone or the more intensive EsPhALL chemotherapy backbone.
- To determine the feasibility of administration of imatinib after allogeneic HSCT in High Risk (HR) Ph+ ALL patients.
- To determine event-free-survival (EFS) of HR pediatric Ph+ ALL patients treated with EsPhALL chemotherapy, HSCT in first complete remission and post-HSCT imatinib.
- To compare rates of Grade 3 or higher infections in SR Ph+ ALL patients between the two randomized arms.

- To evaluate EFS and overall survival (OS) of all eligible Ph+ALL patients

enrolled on the study.

- To evaluate OS in SR Ph+ ALL patients.

- To evaluate OS in HR Ph+ ALL patients.

- To evaluate EFS and OS of all eligible ABL-class fusion positive ALL patients

enrolled on the study.

Study description

Background summary

Approximately 3-5% of pediatric ALL patients present with the Philadelphia chromosome (Ph+ ALL). Historically, patients with Ph+ ALL had a poor prognosis and were considered candidates for allogeneic hematopoietic stem cell transplant (HSCT) in first complete remission (CR1). Studies conducted by COG and the European EsPhALL consortium over the last decade have demonstrated that the majority of pediatric Ph+ ALL patients are effectively treated with the combination of a tyrosine kinase inhibitor (TKI) and chemotherapy, without HSCT in CR1. However, the cytotoxic chemotherapy backbone administered in these trials was more intensive than is standardly used in COG for non-Ph+ pediatric B-ALL, resulting in high rates of treatment-related toxicities (including life-threatening infections) and mortality, as well as increased risk of late effects.

ABL-class fusion positive B-ALL subtypes other than BCR-ABL1 have a biological profile similar to Ph+ ALL. These patients have an overall poor prognosis, with most patients treated with high risk chemotherapy and extensive use of HSCT in CR1 which was associated with a high treatment-related mortality. These patients show favourable response to TKI. This suggests that patients with ABL-class fusion positive ALL may benefit from the treatment strategy adopted for Ph+ ALL.

Reduction in treatment-related toxicities, if achievable without compromising disease-free survival (DFS), would represent an important advance for this patient population. EsPhALL 2017/COG AALL1631 is an international collaborative protocol conducted by COG and EsPhALL.

Study objective

This study has been transitioned to CTIS with ID 2024-515499-12-00 check the CTIS register for the current data.

The primary objective is reducing treatment-related morbidity and mortality without adversely impacting DFS in Ph+ ALL patients, classified as Standard Risk (SR) based on low minimal residual disease (MRD) at week 10-12 of therapy. Because there is variability in clinical practice regarding the use of TKI*s post-HSCT in Ph+ ALL, the feasibility and outcome of post-HSCT imatinib administration in HR pediatric Ph+ ALL patients will be tested.

Study design

Ph+ ALL patients will enter the trial at Day 15 of Induction IA and begin daily imatinib at that time. After the Induction IB phase (week 10-12), MRD will be assessed by immunoglubulin-T-cell-receptor (IgH-TCR) PCR, and patients will be classified as SR (those with MRD < 5 x 10-4) or High Risk (HR; MRD > 5 x 10-4).
SR patients will be randomized to receive one of two cytotoxic chemotherapy backbones: 1) the EsPhALL backbone (Arm A) used in previous EsPhALL protocols and COG AALL1122/CA180372 or 2) a less intensive regimen similar to those typically administered to non-Ph+ ALL HR patients on COG trials (Arm B). Patients on both arms will continue to receive imatinib until the completion of all planned chemotherapy (two years of treatment).
For HR patients (approximately 15-20% of patients), allogeneic HSCT in CR1 is still considered the treatment of choice. HR patients will receive the EsPhALL chemotherapy backbone and proceed to HSCT after completion of the three consolidation blocks.

Intervention

SR patients: imatinib combined with 1) EsPhALL chemotherapy scheme or 2) HR COG-ALL chemotherapy scheme
HR patients: standard imatinib combined with chemotherapy pre-SCT and imatinib post-SCT (standard, no intervention)

Study burden and risks

The treatment in Induction, the standardarm for SR patients, and the treatment of HR patients is considered as best available treatment by the DCOG. There is no increased risk or burden compared to the standard treatment with chemotherapy. In the experimental arm form SR patients a less intensive chemotherapy regimen is given, which may result in less treatment-related toxicity, but also in an increased risk of relapse.
Imatinib is standard treatment for children with Ph+ ALL and is also standard

administered post-SCT in HR patients.

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)

Inclusion criteria

1. Enrollment on National ALL protocol prior to enrollment on EsPhALL2017/COGAALL1631.
2. Age >1 year and <21 years at ALL diagnosis.
3. Newly diagnosed ALL :
a. type B or T or mixed phenotypic acute leukemia (MPAL meeting 2016 WHO definition), with definitive evidence of BCR-ABL1 fusion by karyotype, FISH

and/or RT-PCR
b. type B, with definitive evidence of ABL class fusions (in The Netherlands these patients are treated according to another protocol, and will therefore not be included in the EsPhALL2017/COGAALL1631 trial)
4. Prior therapy for BCR-ABL1 fusion patients:
- Induction therapy which includes vincristine, a corticosteroid, usually PEG-L-Asparaginase, with or without anthracycline, and/or other standard cytotoxic chemotherapy.
- Not received more than 14 days of multiagent Induction therapy beginning with the first dose of vincristine.
- May have started imatinib prior to study entry but have not received more than 14 days of imatinib.
5. Prior therapy for ABL-class patients:
- Must have previously completed the 4 or 5 weeks of multiagent Induction chemotherapy
- May have started imatinib during Induction IA, at the same time of or after the first vincristine dose.
6. Performance status corresponding to ECOG scores of 0, 1, or 2.
7. Adequate liver function.
8. Adequate cardiac function.
9. Adequate renal function.

Exclusion criteria

1. Known history of chronic myelogenous leukemia (CML).
2. ALL developing after a previous cancer treated with cytotoxic chemotherapy.
3. Active, uncontrolled infection or active systemic illness that requires ongoing vasopressor support or mechanical ventilation.
4. Down syndrome.
5. Pregnancy.
6. Breast feeding.
7. Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of treatment according to protocol
8. Patients with congenital long QT syndrome, history of ventricular arrhythmias or heart block.
9. Prior treatment with dasatinib, or any BCR-ABL1 inhibitor other than imatinib.

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):	09-11-2018
Enrollment:	28
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cerubidine
Generic name:	Daunorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cyclophosphamide Sandoz
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Imatinib CF
Generic name:	Imatinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate Sandoz
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine

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

Ethics review

Approved WMO Date:	22-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-03-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	11-03-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2024
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	CTIS2024-515499-12-00
EudraCT	EUCTR2017-000705-20-NL
ClinicalTrials.gov	NCT03007147
CCMO	NL64484.078.18