Treatment study for children and adolescents with Acute Promyelocytic Leukemia

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This study has been transitioned to CTIS with ID 2024-518669-83-00 check the CTIS register for the current data. Primary objective:To assess, in an international pediatric study, the efficacy, in terms of event-free survival, of a combination of ATO...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Observational non invasive

Summary

ID

NL-OMON54336

Source
ToetsingOnline

Brief title
ICC APL Study 02

Condition

- Leukaemias

Synonym
acute promyelocytic leukemia; blood cancer

Research involving
Human

Sponsors and support

Primary sponsor: AIEOP- Associazione Italiana Ematologia Oncologia Pediatrica
Source(s) of monetary or material Support: Ministerie van OC&W,Pfizer

Intervention

Keyword: Acute Promyelocytic Leukemia, Children

Outcome measures

Primary outcome

The primary endpoint of the study is event-free survival (EFS). This cumulative endpoint includes the following events:

• no achievement of hematological complete remission after induction therapy;

• no achievement of molecular remission after three consolidation courses (molecular resistance);

• relapse (hematological/molecular);

• death, including early death, at 2 years from diagnosis.

Secondary outcome

• Rate of hematological CR after induction

• Rate of early and aplastic death during induction

• Overall survival (OS)

• Cumulative incidence of either hematological and molecular relapse (CIR)

• Incidence of hematological and non-hematological toxicity

• Kinetics of MRD clearance

• Rate of molecular remission after 3 consolidation cycles

• Assessment of PML/RARα transcript level reduction during treatment

• Toxicity - hematological and non-hematological

• Supportive care requirements

• Total hospitalization days during therapy and health economic impact

Study description

Background summary

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML). APL is often clinically characterized by the presence of coagulation abnormalities, including mostly hyperfibrinolysis, disseminated intravascular coagulation (DIC), and unspecific proteolysis.
APL represents approximately 4-8% of pediatric AML.
Pediatric patients appear to present more commonly with hyperleukocytosis, as compared to their adult counterparts. Approximately 35-40% of children with APL fall within a HR group defined by a presenting WBC >=10 x 10 9/L, and predicts for poorer outcome.This is due to both an increased risk of induction death, particularly as a result of haemorrhage, and a significantly higher rate of relapse.
Most of current treatment approaches are based on the combination of ATRA and anthracycline-containing chemotherapy. The introduction of ATRA for the treatment of adults and children, led to an increase of remission rates up to 98%, together with a reduction of morbidity and mortality, mostly associated with early fatal coagulopathy. Despite the dramatic improvements achieved in frontline therapy of APL with ATRA plus anthracycline-based regimens, relapses still occur in approximately 20% of patients. Moreover, these regimens are associated with significant toxicities due to severe myelosuppression frequently associated with life-threatening infections and potentially serious late effects, including development of secondary MDS/AML and anthracycline-related myocardiopathy.
In a recent randomized clinical trial conducted in adults in SR APL (WBC at diagnosis < 10 x 10 9/L, APL0406 trial), a combination of arsenic trioxide (ATO) and ATRA has been shown to result into better survival and EFS rates with significantly lower toxicity, compared to the standard ATRA + idarubicin (AIDA) therapy. However, a treatment approach with frontline ATO has been tested in a limited number of pediatric patients.
Inspired by both the results of ICC APL01 and the adult APL0406 trial we intend to perform the first pediatric chemotherapy-free approach testing the combination of ATRA/ATO +/- GO based on risk-stratification, expecting less severe hematologic toxicity and treatment-related mortality, thus resulting in an improved outcome for these children.

Study objective

This study has been transitioned to CTIS with ID 2024-518669-83-00 check the CTIS register for the current data.

Primary objective:
To assess, in an international pediatric study, the efficacy, in terms of

event-free survival, of a combination of ATO and ATRA in newly diagnosed SR APL children and adolescents and to explore the safety and efficacy of a combination therapy comprising ATRA/ATO + GO in HR APL.

Secondary Objectives:
• To evaluate the short- and long-term toxicity profile of ATO in pediatric patients, when combined with ATRA (SR APL) or ATRA plus GO (HR APL)
• To compare the clearance kinetics of minimal residual disease (MRD) with that of the previous AIDA-like protocols, COG protocol and ICC APL Study 01
• To estimate the cumulative incidence of both molecular and hematological relapse
• To calculate the probability of overall survival and the early death rate
• To prospectively evaluate the impact of FLT3-ITD on this patient population
• To compare the duration of hospitalization and quality of life with those of the previous AIDA-like protocols and ICC APL study 01

Study design

The ICC APL Study 02 is an international, multi-center non-randomized study delivering risk-stratified treatment based on the ICC APL 01 Study and experiences from adults on the efficacy of the combination of ATRA plus ATO in SR patients with APL.
The part of the study for HR patients was started after a safety run-in phase enrolling 6 patients. The toxicity data from these 6 patients has been evaluated, and no problems were identified.

Study burden and risks

The introduction of ATRA has been crucial for both antileukemic efficacy in APL and for reducing the early death rate. More recently, ATO, first introduced for treatment of patients with refractory/relapsed PML/RARα positive APL, has been shown to be highly effective for achieving high cure rates in association with reduced toxicity in adults with APL.
In a recent randomized clinical trial in adult patients affected by SR APL showed that a combination of ATO and ATRA offers better survival rates with significantly lower toxicity and better Quality of Life, as compared to the standard ATRA + idarubicin (AIDA) therapy.

Side effects of GO are myelosuppression, allergic reactions and liver toxicity including sinusoidal obstruction syndrome (SOS). GO has been shown to elicit a significant antileukemic activity in AML, being especially active in APL, due to the high expression of the CD33 antigen on APL cells.

We consider treatment according to ICC APL study02 the best available treatment for pediatric APL patients. Therefore this treatment is the standard treatment for these patients in the Netherlands. We expect to see less toxicity as a

result of this treatment.

Contacts

Public
AIEOP- Associazione Italiana Ematologia Oncologia Pediatrica

Via Massarenti 11
Bologna 40138
IT
Scientific
AIEOP- Associazione Italiana Ematologia Oncologia Pediatrica

Via Massarenti 11
Bologna 40138
IT

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Newly diagnosed APL confirmed by the presence of PML/RARα fusion gene
- Age <18 years
- Written informed consent by parents or legal guardians
- If applicable, female participants must have pregnancy test by beta-HCG dosing and be negative.
- Patients of child-bearing or child-fathering potential must be willing to

practice the most appropriate approach for birth control from the time of enrollment in this study and for 3 months after receiving the latest infusion.

Exclusion criteria

- Patients with a clinical diagnosis of APL but subsequently found to lack PML/RARα rearrangement should be withdrawn from the study and treated with an alternative protocol
- Significant liver dysfunction (bilirubin serum levels >3 mg/dL, ALT/AST serum levels >5x the normal values)
- Creatinine serum levels >2 times the normal value for age
- Significant arrhythmias, ECG abnormalities, other cardiac contraindications (L-FEV <= 50% or LV-FS <=28%)
- Neuropathy grade 2 or greater
- Concurrent active malignancy
- Uncontrolled life-threatening infections
- Pregnant or lactating females
- Patients who had received alternative therapy (APL not initially suspected; ATRA and/or ATO not available)

Study design

Design

Study phase:	2
Study type:	Observational non invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-07-2024
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Arsenic Trioxide
Generic name:	Arsenic Trioxide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cytarabin
Generic name:	Cytarabin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	Methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Mylotarg
Generic name:	Gemtuzumab Ozogamicin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vesanoid
Generic name:	Tretinoin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-02-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-05-2023
Application type:	First submission
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	CTIS2024-518669-83-00
EudraCT	EUCTR2017-002383-40-NL
CCMO	NL72509.041.21