A randomized phase 3 trial of fludarabine/cytarabine/gemtuzumab ozogamicin with or without venetoclax in children with relapsed AML

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This study has been transitioned to CTIS with ID 2023-510160-12-00 check the CTIS register for the current data. To assess if venetoclax combined with FLA+GO (fludarabine, high-dose cytarabine, and gemtuzumab ozogamicin) will improve overall...

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

Summary

ID

NL-OMON51670

Source
ToetsingOnline

Brief title
VENPedAML, Venetoclax in children with relapsed AML, ITCC-101/APAL2020D

Condition

- Leukaemias

Synonym
Acute myeloid leukemia, bone marrow cancer

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie

Source(s) of monetary or material Support: AbbVie B.V.,AbbVie;Prinses Máxima centrum en Leukemia & Lymphoma Society

Intervention

Keyword: Leukemie/AML, pediatric and young adults, phase III, venetoclax

Outcome measures

Primary outcome

The primary endpoint of the study is overall survival (OS). OS is defined as time from randomization until death of any cause. Patients still alive at the time of clinical cutoff date will be censored at their last known alive date.

Secondary outcome

Morphology and flow-based event-free survival (EFS): days from date of randomization to the first event (subsequent relapse after ped-flow and ped-morph CR, death of any cause, failure to achieve remission (ped-flow and ped-morph CR, CRp or CRi) after 2 cycles of treatment, or secondary malignancy). Patients who are event-free will be censored at date of last adequate disease assessment. Pediatric flow and morphologic treatment failure (defined by morphology and flow as not achieving remission after two cycles in separate analyses) is calculated as an event at day 1.

Flow-based overall response rate (ORR)

Morphological ORR

Duration of response (DOR): Time from documentation of disease response

(ped-flow CR/CRp/CRri or ped-morph CR/CRp/CRi) to disease progression or death of disease, whichever occurs earlier.

Cumulative incidence of relapse (CIR): Estimate of the risk that a patient will develop a relapse during a specified period of time.

Non-relapse mortality (NRM): Death without recurrence or progression of disease during treatment.

Hematopoietic stem cell transplantation (HSCT) rate: The rate of those proceeding to subsequent hematopoietic stem cell transplantation as consolidation therapy is calculated as the number of patients who receive a hematopoietic stem cell infusion divided by the total number of patients enrolled.

Safety

Pharmacokinetics (PK) of venetoclax in blood in combination with intensive chemotherapy and GO.

Pediatric Minimal Residual Disease (Ped-MRD) negative ped-flow is defined as patients obtaining ORR (CR/CRp/CRri:) CR/CRp/CRi with no detectable residual disease defines asand <0.1% leukemic blasts in a cellular BM by central flow

cytometry.

To compare the morphological International Working Group complete response

(IWG-CR) rate in patients receiving FLA+GO with and without venetoclax.

Study description

Background summary

Although the prognosis of children with acute myeloid leukemia (AML) has improved over the last decades, with overall survival (OS) rates approaching 70% as a result of intensive frontline treatment, aggressive salvage therapy following relapse and improvements in supportive care, outcome after relapse remains poor. The 4-year probability of survival (pOS) of children with AML in 1st relapse is 38% and the recommended treatment approach for first relapse includes an anthracycline-based re-induction followed by a second cycle of chemotherapy and HSCT, based on the results of the iBFM AML 2001/01 using FLAG-liposomal daunorubicin in 1st cycle, and FLAG in second cycle, followed by allogenic transplantation. In the iBFM AML 2001/01 study, one-year OS of early first relapse was 52% and late relapse of 66%. However, options for patients unable to tolerate anthracyclines in first relapse are limited.
For patients beyond first relapse, limited data exist. The AML-BFM study group reported that survival of children with AML in 2nd relapse was poor, with a 5-year pOS of approximately 15% and 31 following HSCT (n=25/73). Early second relapse (within one year after first relapse) was associated with dismal outcome (pOS 2%, n=44 vs. 33%, n=29; p<0.0001). There is no consensus on the therapy recommended in the 2nd relapses of AML in children. Additional therapeutic options for children in 2nd relapsed AML, and children in 1st relapse unable to tolerate anthracycline, are needed.
Based on the promising results of the phase I/II VENAML trial shown below, off-label use of venetoclax in children with relapsed AML in the United States is more and more frequent. A randomized trial of venetoclax in combination with intensive chemotherapy in children with 2nd relapsed AML and 1st relapsed AML unable to receive additional anthracycline would inform and evaluate if this agent is an effective option for this population to improve its poor prognosis.

Study objective

This study has been transitioned to CTIS with ID 2023-510160-12-00 check the CTIS register for the current data.

To assess if venetoclax combined with FLA+GO (fludarabine, high-dose cytarabine, and gemtuzumab ozogamicin) will improve overall survival of children with relapsed acute myeloid leukemia (AML) compared to FLA+GO .

Study design

This is an open-label phase 3 randomized multicenter international trial in children with relapsed acute myeloid leukemia (AML), to assess if venetoclax combined with FLA+GO (fludarabine, high-dose cytarabine, and gemtuzumab ozogamicin) will improve overall survival compared to FLA+GO.

Intervention

This is an open-label randomized phase 3 study. Patients receiving venetoclax will receive adult equivalent dosages, either based on age (less than 2 years) or weight (2 years and older), unless dose reductions are required for toxicity management. Patients will take venetoclax for 21 days in two cycles. In the first cycle, a dose ramp-up is applied for venetoclax, and in bridging/maintenance courses the venetoclax dose is adapted when used in combination with azacitidine.
Venetoclax will be provided by AbbVie as 10 mg, 50 mg, and 100 mg tablets, and 3 mg, 10 mg, 25 mg, 100 mg and 600 mg powder sachets for oral suspension that will be used to administer PO 300 mg adult equivalent dose on Cycle 1 Day 1 and 600 mg adult equivalent dose on subsequent days. Note that in maintenance a lower dose of venetoclax is applied in combination with azacitidine, i.e., 400 mg adult equivalent dose.
A 2-day ramp-up is proposed in this study, based on the observed low rates of TLS in both the M13-833 and VENAML studies, and the use of a 2-day ramp up in the VENAML trial, in which the ramp up was well-tolerated. Additionally, the shorter ramp up enables patients to benefit from the target dose of Venetoclax more rapidly by minimizing the time during which AML can progress.

FLA/GO will be given at regular doses, therefore there is no undertreatment in terms of chemotherapy, and Venetoclax may be added to this.

Study burden and risks

Participation in this trial can induce regular AML chemotherapy side effects, including added side effects from venetoclax, including potentially unknown side effects. Since there is no validated biomarker that can predict response, we opted for a randomized study without applying a selection biomarker. Dosing of venetoclax was tested and considered safe in a prior pediatric study in combination with high-dose chemotherapy in a similar population of relapsed pediatric AML patients.
Given the poor outcome of 2nd relapse patients and the improvements in stem cell transplantation (with the option to provide for example a 2nd or even 3rd

HSCT where needed) it offers novel option for patients who desire treatment with curative intent, who would otherwise probably be offered chemotherapy such as FLA or FLA/GO as regular care. The study will assess whether venetoclax has added value on top of background chemotherapy, and will be the largest second relapse study performed to date, and hence will be an important point of reference for future studies as well, in a similar fashion as the study AML 2001/01 by Kaspers et al in 1st relapse. Some patients may opt out or it may not be feasible to offer them another round of intensive treatment due to existing organ-toxicity, and such patients will be treated according to patient and physician preference, including the possibility of palliative care or *palliative chemotherapy* only.
Patients will undergo some additional tests as required per protocol, i.e., pregnancy tests (if applicable). Moreover patient and/or parents or legal guardians will be asked to participate in ancillary studies, especially PK and some PD studies. This will require additional blood sampling, which is performed either through the available central line, already in place for all patients, or via venipuncture only in case there is no available central line, and only in the venetoclax arm. Given the intensity of AML treatment and the requirement for regular transfusions the burden regarding the additional blood volume is considered limited, and within keeping with EMA guidelines on blood sampling volumes.
Most of the hospital stays and outpatient visits and monitoring of treatment response are according to standard of care in this population and would also have occurred outside this study. Nevertheless, investigators at the sites are encouraged to perform the invasive procedures (e.g., bone marrow aspirate, lumbar puncture, blood sampling, nasogatric tube insertion) in a way to minimize the discomfort and pain to the patients.
In this study, next-generation sequencing (NGS) will be performed using bone marrow samples to identify AML genetic variation. When there is suspicion of germline variants this will be communicated to the treating physician, and patients and/or parents or legal guardians(s) can decide if they want further testing after consultation with a clinical geneticist.
Considering the SARS-CoV-2 or COVID-19 pandemic, the benefit and risk to patients participating in this study has been considered. Based on the population and disease being studied, it is anticipated that COVID-19 related risks are not expected to differ substantially between study participants and the broader population of pediatric patients receiving treatment for AML. Therefore, no change to the benefit/risk balance for study participants in this study is expected, section 1.4.3 of the protocol.
A stopping rule is included in the study, based on toxic mortality and the incidence of grade 3-4 or higher targeted toxicities (e.g., renal failure, hepatotoxicity). An external Data Safety Monitoring Board (DSMB) will be installed for this study, consisting of an adult hematologist, a pediatric oncologist and an independent statistician, to monitor safety.
Taken together, we feel that the benefit-risk ratio for patients participating in this study is favorable for patients seeking treatment with a curative approach.

Contacts

Public
Prinses Máxima Centrum voor Kinderoncologie

Heidelberglaan 25
Utrecht 3584 CS
NL
Scientific
Prinses Máxima Centrum voor Kinderoncologie

Heidelberglaan 25
Utrecht 3584 CS
NL

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

Patient must have the following:
a. Children, adolescents, and young adults with acute myeloid leukemia without demonstrated FLT3/ITD mutation. Ideally, the status of the mutation needs to be proven in the current relapse. Nevertheless, patients with previous FLT3/ITD negative test from prior lines can be included based on local results in order to not delay the start of treatment.
b. And patients must have AML which is either:
- untreated second relapse, in patients who are sufficiently fit to undergo another round of intensive chemotherapy, or

- untreated first relapse, in patients who cannot tolerate additional anthracycline containing chemotherapy per investigator discretion.

Patients must have a performance status corresponding to ECOG scores of 0, 1 or 2 (>= 50% Lansky or Karnofsky score)

Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the minimum duration from prior anti-cancer directed therapy prior to enrolment (more details in the protocol).
Cytotoxic chemotherapy: Must not have received cytotoxic chemotherapy within 14 days prior to start of protocol treatment, except for corticosteroids, low dose cytarabine or hydroxyurea (see below) that can be given up to 24 hours prior to start of protocol treatment.
Antibodies: >= 21 days must have elapsed from infusion of last dose of an antibody-drug conjugate prior to start of protocol treatment.
Interleukins, Interferons and Cytokines : >= 21 days after the completion of interleukins, interferon or cytokines
Hematopoietic growth factors: >= 14 days after the last dose of a longacting growth factor or >=7 days for short-acting growth factor prior to start of protocol treatment.
Radiation therapy (RT): Between 14 and 84 days depeding on the extent of radiation fields
Stem Cell Infusions: >= 84 days since allogeneic bone marrow or stem cell transplant or boost infusion. No evidence of active graft versus host disease
Patients must be off medications to treat or prevent either graft-versushost disease post bone marrow transplant or organ rejection posttransplant for at least 14 days
Cellular Therapy: >= 42 days after the completion of any type of cellular Therapy

Adequate organ function.
a. Adequate Renal Function defined as:
• Calculated eGFR (based on Schwartz formula) or radioisotope GFR >= 60ml/min/1.73 m2, OR •A serum creatinine based on age/sex
b. Adequate Liver Function defined as:
•Total or direct (conjugated) bilirubin <= 1.5xULN, AND •Alkaline phosphatase <= 2.5xULN, AND
•SGPT (ALT) <= 2.5xULN oIf liver abnormality is due to radiographically identifiable leukemia infiltrate, the patient will remain eligible.
c. Cardiac performance: Minimum cardiac function defined as:
•No history of congestive heart failure in need of medical treatment
•No pre-treatment diminished left ventricular function on echocardiography (FS <25% or EF <40%)
•No signs of congestive heart failure at presentation of relapse.

Patient, parent or legal guardian must sign and date informed consent and pediatric assent (when required), prior to the initiation of screening or study

specific procedures, according to local law and legislation

Exclusion criteria

D5a. In het Engels
1) General exclusion criteria
a. Patients who in the opinion of the investigator, may not be able to comply with the study requirements of the study, are not eligible.

b. Patients with Down syndrome.

c. Patients with Acute promyelocytic leukemia (APL) or Juvenile myelomonocytic leukemia (JMML).

d. Patients with isolated CNS3 disease or symptomatic CNS3 disease.

e. Patients with malabsorption syndrome or any other condition that precludes enteral administration of venetoclax.

f. Patients who are currently receiving another investigational drug other than those specified for this study (venetoclax and GO are considered investigational in this study).

g. Patients with Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known congenital bone marrow failure syndrome.

h. Patients with known prior allergy to any of the medications used in protocol therapy.

i. Patients with documented active, uncontrolled infection at the time of study entry.

j. Known hepatitis C virus (HCV), hepatitis B virus (HBV) (known positive hepatitis B virus (HBV) surface antigen (HBsAg) result) or human immunodeficiency virus (HIV) infection. Note: For the countries under EU CTR, these tests are required at screening. For other countries, HCV, HBV, and HIV testing does not need to be conducted at screening unless it is required per local guidelines or local regulations.

2) Concomitant Medications

a. Patients who have received strong and moderate CYP3A inducers such as rifampin, carbamazepine, phenytoin, and St. John*s wort within 7 days of the start of protocol treatment.

b. Patients who have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit within 3 days of the start of protocol treatment.

c. Patients who are hypersensitive to the active substance or to any of the excipients listed in the summary of products characteristics (SPC) or US prescribing information per local label.

3) Pregnancy or Breast-Feeding:
a. Patients who are pregnant or breast-feeding.

b. Patients of reproductive potential may not participate unless they have agreed to use a highly effective contraceptive method per Clinical Trial Facilitation Group (CTFG) guidelines for the duration of study therapy at least 30 days after last dose of venetoclax, or 7 months after gemtuzumab ozogamicin treatment, or for 6 months after the completion of all study therapy, whichever is longer

c. Male patients must use a condom during intercourse and agree not to father a child or donate sperm during therapy and for the duration of study therapy and at least 30 days after last dose of venetoclax or 4 months after last dose of gemtuzumab ozogamicin, 6 months from the last dose of cytarabine, or 90 days after last exposure to any other chemotherapy, whichever is longer.

Gemtuzumab ozogamicin should not be given:
• to patients with history of veno-occlusive disease (VOD)/Sinusoidal obstruction syndrome (SOS) grade 3 or 4
• to patients with CD33 negative leukemic blasts (determined at local lab)
These patients are eligible for the study but will not be treated with gemtuzumab ozogamicin.

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):	08-02-2023
Enrollment:	5
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Mylotarg
Generic name:	Gemtuzumab ozogamicin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Venclyxto
Generic name:	Venetoclax
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	08-12-2021
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	17-02-2022
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	01-05-2022
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	22-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2024
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	CTIS2023-510160-12-00
EudraCT	EUCTR2021-003212-11-NL

Register	ID
ClinicalTrials.gov	NCT05183035
CCMO	NL79147.041.21