A Phase Ib study of Vyxeos® (liposomal daunorubicin and cytarabine) in combination with Clofarabine in children with relapsed/refractory AML, ITCC-092

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This study has been transitioned to CTIS with ID 2023-508050-26-00 check the CTIS register for the current data. Primary objective:•To establish the recommended phase 2 dose of Vyxeos®/CPX-351 in combination with clofarabine in children with...

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

Summary

ID

NL-OMON55064

Source
ToetsingOnline

Brief title
Vyxeos® with Clofarabine for pediatric AML

Condition

- Leukaemias

Synonym
relapsed/refractory pediatric acute myeloid leukemia; children with a specific type of blood cancer that has returned or is persistent

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Erasmus MC Rotterdam,Jazz Pharmaceuticals

Intervention

Keyword: clofarabine, liposomal daunorubicin and cytarabine, pediatric AML, relapsed/refractory

Outcome measures

Primary outcome

Frequency of Dose-limiting toxicities (DLTs) during the first course of

therapy.

Secondary outcome

1. Safety and tolerability: frequency of AEs, frequency of laboratory

abnormalities and number of toxic deaths

2. Measures of anti-leukemic activity: ORR after 1 course and as best response

and ORR after 2 courses, which includes CR, CRi, and PR, determined by

morphology with flow cytometric confirmation.

3. Overall patient survival (OS) and relapse-free survival

4. Number of patients undergoing HSCT after treatment

Exploratory endpoints:

5. Serum and intracellular (as Ara-CTP accumulation in leukemic blasts)

pharmacokinetic parameters

6. Relationship between response (ORR) and Ara-CTP accumulation

7. Correlation between duration of response and measurable residual disease

(MRD) assessed by Flow-cytometry

Study description

Background summary

Treatment with intensive chemotherapy in AML results in approximately 70% survival in newly diagnosed patients. Prognosis at relapse is worse and is in the 30-40% range. Relapse treatment generally consists of one course of fludarabine, cytarabine and liposomal daunorubicin (FLAG-DNX), followed by a fludarabine and cytarabine course and subsequent stem-cell transplantation. Cytarabine has been used in combination with fludarabine and cladribine, with the aim to induce synergism by increasing Ara-CTP (active cytotoxic metabolite from ara-C) accumulation, which can be seen as a surrogate marker for cytarabine induced cell-kill. Synergy with cytarabine can also be achieved with clofarabine, which is a potent inhibitor of ribonucleotide reductase, leading to a depletion of normal deoxynucleotides and subsequently to increased Ara-CTP levels.

The phase IB trial ITCC020/I-BFM 2009-02 recently reported that clofarabine, replacing fludarabine in the standardly used fludarabine, cytarabine and liposomal daunorubicin (FLAG-DNX) combination regimen, showed high response rates (Overall Response Rate - ORR 68% and 80% at the recommended phase 2 dose - RP2D) in patients with refractory/relapsed AML, and was generally tolerable, with infectious complications as the main side-effect due to the immunosuppressive properties of clofarabine.

Currently DNX is unavailable, which urges the need to develop other treatment blocks. The liposomal formulation of Vyxeos®/CPX-351 may be a suitable replacement for DNX, considering the long-term side effect of cardiotoxicity due to anthracyclines which is of primary importance in younger heavily pre-treated patients. Preliminary results in pediatric and young adult patients with relapsed/refractory AML in a COG study using Vyxeos®/(CPX-351) at a RP2D of 135 U/m2 (AAML1421) showed encouraging ORR (80%), with 70% of patients reaching CR/CRi as best response after single agent-treatment with Vyxeos®/ CPX-351. Preclinical data have also assessed an increased Ara-CTP accumulation and cytotoxicity in immortalized cell lines, and confirmed by tests in ex-vivo blasts from a cohort of AML patients (n=5), when cells were exposed to CPX-351 after 4 hours of incubation with fludarabine.

In this study we therefore evaluate Vyxeos®/CPX-351 in combination with clofarabine in a phase 1b study with the aim to establish the RP2D of this combination.

Study objective

This study has been transitioned to CTIS with ID 2023-508050-26-00 check the CTIS register for the current data.

Primary objective:
•To establish the recommended phase 2 dose of Vyxeos®/CPX-351 in combination with clofarabine in children with relapsed/refractory AML

Secondary objectives:
•To determine the safety and tolerability of this combination
•To determine the (preliminary) efficacy in terms of the hematological remission rate in these patients as determined by morphology with flow cytometric confirmation.
•To describe the durability of response, including the number of patients that undergo stem- cell transplant after re-induction with this regimen

Exploratory objectives:
• To describe the serum and intracellular pharmacokinetics parameters of CPX-351 in combination with clofarabine.
• To describe the relationship between response (ORR) and intracellular Ara-CTP accumulation
• To describe the correlation between duration of response and measurable residual disease assessed by Flow-cytometry

Study design

This is an open label, non-randomized, Phase 1b dose-finding study following a Rolling-6 design, with a dose escalation part followed by an expansion cohort to better characterize safety at the RP2D. CPX-351 is the investigational medicinal product in this study and will be made available by Jazz Pharmaceuticals for this study. Clofarabine should be used from commercial stock according to the Summary of Product Characteristics (SPC).

Intervention

Treatment will consist of 2 courses. A combination of Vyxeos®/CPX-351 given at day 1, 3, 5 with clofarabine given at day 2-6 will be administered in course 1, and Vyxeos®/CPX-351 only in course 2.

The infusion schedule for Course 1 is as follows:
• Vyxeos®/CPX-351 ® will be infused over 90 minutes on day 1, 3 and 5 only, 3 hours after the end of clofarabine administration if given on the same day.
• Clofarabine infusion will be given over 2 hours IV, daily on day 2-6.

In Course 2, Vyxeos®/CPX-351 will be administered as single-agent, at the same

DL and with the same infusion schedule of Course 1.

Study burden and risks

The invasive procedures related to the study are the same expected as per standard of care. Patients will undergo some additional tests required per protocol, i.e. pregnancy tests, if applicable, PK samples collection (which are performed through the available central line already in place for all patients).
Risks associated with this study are mainly the anticipated side-effects of Vyxeos®/CPX-351 in combination with Clofarabine. The major toxicities expected by both compounds are related to prolonged myelosuppression and subsequent possible (fungal) infections.
In the ITCC020/I-BFM 2009-02 study with Clofarabine, 3 pulmonary aspergillosis occurred in 34 patients included; therefore to mitigate the risk in the current study we planned to screen patients with CT thorax and galactomannan antigen before the enrollment. In the COG Vyxeos®/CPX-351 study, toxicity was consistent with historical intensive AML regimens, but the number of pediatric patients treated with this compound is still limited. In addition Vyxeos®/ CPX-351 has not been combined before with clofarabine.
To mitigate the overlapping hematologic toxicity, we will test only the approved dose of Vyxeos®/CPX-351 for adults (at 44 mg/m2 of Daunorubicin and 100 mg/m2 of Cytarabin/dose) with increasing dosages of Clofarabine, starting from DL1 with a 50% lower dose of clofarabine compared to the RP2D established in the ITCC020/I-BFM 2009-02.
Prognosis for relapsed/refractory AML is dismal and in the 30-40% range and historical regimens for these patients are intensive. Considering to potentially improve the outcome with this new regimen and expecting comparable toxicity with other available treatments, we think that the potential benefits of the study outweigh the potential toxicity in these patients. Regarding long-term cardiotoxicity, the study regimen can provide additional benefit compared to other available regimens, since liposomal daunorubicin (DNX) is currently unavailable. The liposomal formulation of Vyxeos®/CPX-351 can replace the benefit of DNX in terms of long-term cardiac toxicity, which is of primary importance in younger pre-treated patients. However, there are no data as yet on long-term cardiac follow-up after using DNX instead non-liposomal formulation of anthracyclines. In the COG Phase I study of Vyxeos®/CPX-351, 1 grade 3 cardiotoxicity was registered.
Toxicity will be closely monitored and if necessary the study will be stopped due to significant safety concerns in accordance with the early stopping rules. Sites will be prompted to collect data on toxicity.

Contacts

Public

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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

• Age >=1 year and <=21 years
• Any >= 2nd relapse of AML
• Refractory AML (defined as >= 20% blasts in the bone marrow after standard (re-) induction therapy)
• Early 1st relapse (defined as relapse within one year from initial diagnosis) of AML
• Any relapse of AML after prior allogeneic HSCT
• Any relapse of AML with high risk cytogenetic characteristics (as defined in Appendix V)

• Complete initial work-up within 7 days prior to study entry, including bone-marrow aspiration, lumbar puncture (without intrathecal therapy)
• Lansky play score >= 60 for patients <16 years of age; or Karnofsky

performance status >= 60 for patients >= 16 years of age (see Appendix I for Performance scales).
• Life expectancy > 6 weeks
• The patient must have a calculated GFR >= 70mL/min/1.73 m2.
• Liver function: total serum bilirubin <= 3 mg/dl or 50 µmol/L and aspartate transaminase (AST) and alanine transaminase (ALT) <=200 U/L
• Adequate cardiac function (defined as shortening fraction >=28% or ejection fraction >=50%)

• For female patients with childbearing potential, a negative test for pregnancy is to be performed before entry on study.
• Male and female patients must use a highly effective contraceptive method during the study and for a minimum of 6 months after study treatment.
• Female patients may not breastfeed during the study and for a minimum of 3 months after study treatment.
• Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule is required; those conditions should be discussed with the patient before registration in the trial.
• Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations.

Concomitant treatments:
• Concomitant administration of any other experimental drug under investigation, or concurrent treatment with any other anti-cancer therapy other than specified in the protocol is not allowed.
• GCSF will not be used for priming and no routine GCSF support is allowed during the 1st course, except for life-threatening infections.

Additional criteria:
• At least 6 patients must be enrolled with an M3 or a WBC count >10x109/L with blasts

Exclusion criteria

• Evidence of a currently uncontrolled bacterial, viral or parasitic infection
• Evidence of a fungal infection, defined as either:
- Pulmonary infiltrates suggestive of a fungal infection at HR-CT (within 3 weeks prior to enrollment) - Positive Aspergillus serum test (galactomannan), according to local laboratory practice (within 3 weeks prior to enrollment)
• Evidence of isolated extramedullary relapse, including isolated CNS-relapse
• Evidence of CNS3 or symptomatic CNS leukemia
• Down Syndrome
• Evidence of relapsed/refractory acute promyelocytic leukemia (APL)
• Use of any anticancer therapy within 2 weeks before study entry. The patient

must have recovered from all acute toxicities from any previous therapy (note: hematological toxicities do not need to be considered since the patient has overt leukemia)
• History of prior veno-occlusive disease (VOD)
• Known hypersensitivity to cytarabine, clofarabine or liposomal daunorubicin
• Copper metabolism deficiency, such as Wilson's disease

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-01-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evoltra
Generic name:	Clofarabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Vyxeos liposomal
Generic name:	Daunorubicin and cytarabine (liposomal)
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-06-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-09-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	23-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-12-2021

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-04-2022
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	CTIS2023-508050-26-00
EudraCT	EUCTR2020-000142-34-NL
CCMO	NL72866.041.20
Other	NL8134