Vyxeos® and Clofarabine in relapsed/refractory pediatric AML

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20809

Source
Nationaal Trial Register

Brief title
VyClo study

Health condition

relapsed/refractory AML (pediatric)

Sponsors and support

Primary sponsor: Princess Máxima Center for pediatric oncology
Source(s) of monetary or material Support: Jazz Pharmaceuticals, Princess Máxima Center for pediatric oncology

Intervention

Outcome measures

Primary outcome

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

Secondary outcome

• 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

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 in Europe, 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 Vyxeos®/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

A safe RP2D of Vyxeos®/CPX-351 in combination with clofarabine can be identified in this phase 1b study.

Study design

C1D1, C2D1, 4 weeks after C2D28 (EOT)

Intervention

Combination treatment is allowed only for Course 1: An adapted regimen is used to combine Vyxeos®/CPX-351 given at day 1, 3, 5 with clofarabine given at day 2-6.
- Vyxeos®/CPX-351 will be infused on day 1, 3 and 5 only, 3 hours after the end of clofarabine (if on the same day).
- Clofarabine infusion will be given daily on day 2-6.
- CNS prophylaxis (recommended) on day +6.

Patients may repeat one course of Vyxeos®/CPX-351 as single agent in Course 2, in the absence of significant safety concerns or progressive disease:
- Vyxeos®/CPX-351 will be administered alone, at the same dose level and with the same infusion schedule of Course 1
- CNS prophylaxis IT therapy, is recommended and scheduled at day 1 of course 2.

Contacts

Public
Prinses Máxima Centrum voor kinderoncologie
Miriam Stumpf

+31 650006609
Scientific
Prinses Máxima Centrum voor kinderoncologie
Miriam Stumpf

+31 650006609

Eligibility criteria

Inclusion criteria

We will include pediatric patients ≥1 year and <21 years with:
• Any ≥ 2nd relapse of AML

• Refractory AML (defined as ≥ 20% blasts in the bone marrow after standard induction therapy)
• Early 1st relapse (defined as relapse within one year from initial diagnosis) of AML
• Any relapse of AML after prior allogenic HSCT
• Any relapse of AML with high risk cytogenetic characteristics (as defined in protocol Appendix V)

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
Initial work-up:
• Complete initial work-up within 7 days prior to study entry, including bone-marrow aspiration, lumbar puncture (without intrathecal therapy)
General conditions:
• Lansky play score ≥ 60; or Karnofsky performance status ≥ 60
• Life expectancy > 6 weeks
• The patient must have a radioisotope GFR ≥ 70mL/min/1.73 m2.
• Liver function: serum bilirubin ≤3 × upper limit of normal (ULN) and aspartate transaminase (AST)/alanine transaminase (ALT) ≤5×ULN
• Adequate cardiac function (defined as shortening fraction ≥28% or ejection fraction ≥50%)
• No evidence of a currently uncontrolled bacterial, viral or parasitic infection
• No 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)
• No evidence of isolated extramedullary relapse, including isolated CNS-relapse
• No evidence of CNS3 or symptomatic CNS leukemia
• No presence of Down Syndrome
• No evidence of relapsed/refractory acute promyelocytic leukemia (APL)
• No 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)
• No history of prior veno-occlusive disease (VOD)
• No known hypersensitivity to cytarabine, clofarabine or liposomal daunorubicin
Other:
• 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.
• 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/randomization, 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

see inclusion criteria

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-11-2020
Enrollment:	25
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	31-10-2019
Application type:	First submission

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
NTR-new	NL8134
Other	METC Utrecht : not known yet

Study results