Vyxeos® and Clofarabine in relapsed/refractory pediatric AML

Gepubliceerd: 31-10-2019 Laatst bijgewerkt: 13-12-2022

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

Ethische beoordeling	Positief advies
Status	Werving gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON20809

Bron
Nationaal Trial Register

Verkorte titel
VyClo study

Aandoening

relapsed/refractory AML (pediatric)

Ondersteuning

Primaire sponsor: Princess Máxima Center for pediatric oncology
Overige ondersteuning: Jazz Pharmaceuticals, Princess Máxima Center for pediatric oncology

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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

Onderzoeksopzet

C1D1, C2D1, 4 weeks after C2D28 (EOT)

Onderzoeksproduct en/of interventie

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.

Contactpersonen

Publiek

Prinses Máxima Centrum voor kinderoncologie
Miriam Stumpf

+31 650006609

Wetenschappelijk

Prinses Máxima Centrum voor kinderoncologie
Miriam Stumpf

+31 650006609

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

see inclusion criteria

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	06-11-2020
Aantal proefpersonen:	25
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	31-10-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8134
Ander register	METC Utrecht : not known yet

Resultaten