A phase II study of clofarabine in combination with cytarabine and daunoxome for children with acute myeloid leukemia withour other treatment options.

Gepubliceerd: 25-06-2009 Laatst bijgewerkt: 18-08-2022

This is a dose-escalation study to determine the safe dose of clofarabine given in combination with cytarabine and liposomal daunorubicin.

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

Samenvatting

ID

NL-OMON22399

Bron
NTR

Verkorte titel
CLARA-DNX

Aandoening

acute myeloid leukemia in children
relapse
refactory

Ondersteuning

Primaire sponsor: Erasmus MC, Rotterdam, The Netherlands
Overige ondersteuning: Stichting Kinderen Kankervrij en Genzyme

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To establish the recommended dose of clofarabine in combination with cytarabine and liposomal daunorubicin (DaunoXome®) in children with relapsed/refractory AML, based on the FLAG regimen as used in the Relapsed AML 2001/01 study.

Toelichting onderzoek

Achtergrond van het onderzoek

AML is a rare disease, and accounts for approximately 20% of pediatric leukemias. Treatment with intensive chemotherapy results in approximately 60-70% survival in newly diagnosed patients.

Prognosis at relapse is worse, and is in the 30-40% range. A couple of years ago an international relapse study was opened asking a randomized question in relapsed/refractory AML (study relapsed AML 2001/01). This randomization concerned the superiority of the FLAG regimen in combination with DaunoXome® (liposomal daunorubicine) versus FLAG alone, and is still ongoing. Overall results show that poor response to the 1st course of therapy (>20% of blasts in the BM shortly before the 2nd course), was seen in 23% of patients, and more often in early relapses (31%) than in late relapses (15%). Early death occurred in 6% of patients. Complete remission (CR) was achieved in 63% of patients after 2 courses, and these patients have a probability of survival at 3 years of 47%, compared to 33% for the total group, and only 8% for patients not achieving CR. Compared to early relapses, patients with late relapse had higher CR rates (76 vs. 51%), and higher 3-yr probability of survival of 42% vs. 23%. Clearly, nor the induction nor the consolidation chemotherapy is effective enough - and we need new and better treatment options for these children.

Cytarabine (Ara-C) and the anthracyclines are the back-bone of pediatric AML treatment. Cytarabine can be given in various different schedules, including higher-dose regimens such as 1-3 gr/m2 IV every 12 hours for 3 consecutive days, but also as a lower dose continuous IV schedule (0.5 gr/m2 CI over 24 hours x 4 days). Cytarabine has been used in combination with fludarabine and cladribine, with the aim to induce synergism by increasing Ara-CTP accumulation, which can be seen as a surrogate marker for cytarabine induced cell-kill.
In the current European relapsed AML study, the FLAG (fludarabine 30 mg/m2/day x5 days, Ara-C 2 gr/m2 bolus IV in 3 hours, 4 hours following fludarabine, for 5 days; plus GCSF)

regimen is used as standard re-induction therapy. 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. In the experimental arm of the European relapsed AML protocol liposomal daunorubicin is added. This drug was chosen for its favorable toxicity profile, in particular the expected lack of long-term cardiac toxicity, which is of serious concern for those who survive relapsed AML given the cumulative anthracycline dose these patients may have received during their treatment. The current dose we use is 60 mg/m2 on days 1, 3 and 5 of the FLAG-regimen.

Clofarabine has been tested in phase I/II studies in children with AML. For clofarabine, the DLT was hepatic toxicity and rash, and the MTD for children was defined as 52 mg/m2/day x 5 days per block. Clofarabine is myelo-suppressive, and minimal neurotoxicity has also been reported. The response rate to clofarabine as a single agent in children with AML was relatively low, but this is probably related to the very heavy pre-treatment status of these children, and patients were transplanted in aplasia before proper response determination could take place. Adult AML data do show that the drug is active in AML, even at dosages from 15-20 mg/m2 onwards. Clofarabine has also been studied in combination with cytarabine in adults.

Several pediatric studies are ongoing in the US, evaluating clofarabine in combination with 1) cyclophosphamide; 2) cyclophosphamide and etoposide and 3) cytarabine 1 gram/m2 x 5 days, either in ALL or AML. The combination studies with cyclophosphamide have caused some toxicity concerns, especially hepatotoxicity.

We aim at developing a combination of clofarabine, cytarabine and DaunoXome®, based on the FLAG regimen, which is a combination that may be taken forward in the new European relapsed AML protocol, or in other studies.

In the adult studies the combination of cytarabine and clofarabine has been safe, using cytarabine 1 gr/m2 for 5 consecutive days on day 1-5, and clofarabine at 40 mg/m2 for 5 days on day 2-6. This is the same schedule as the COG is currently testing in children. No data on combination studies with anthracyclines are available as yet, but there is extensive experience with the FLAG regimen in combination with anthracyclines such as idarubicin or DaunoXome®.

We propose to use the cytarabine dose as administered in the FLAG regimen (2 gram/m2 bolus IV) – which will also allow a fair comparison with the FLAG regimen in later studies. This regimen is currently being tested in a trial in the USA in adults with relapsed/refractory AML by Agura et al., with a dosing regimen of cytarabine 2 gr/m2/day IV over 3 hours with clofarabine 40 mg/m2/day over 2 hours, daily, for 5 consecutive days. Considering GCSF priming, there are only data available in adults, with various results. As we expect that

priming will in the future be done with CXCR4 inhibitors, and given the lack of hard evidence that GCSF priming works, we decided against using GCSF priming in this study.

Participating countries:

1. Austria (Vienna);

2. Czech Republic (Prague);

3. France (Lyon, Paris (Trousseau and St Louis));

4. Germany (Berlin, Frankfurt, Freiburg, Hannover, Munich, Munster);

5. Italy (Monza, Pavia).

Doel van het onderzoek

This is a dose-escalation study to determine the safe dose of clofarabine given in combination with cytarabine and liposomal daunorubicin.

Onderzoeksopzet

CR rate after 1 course of treatment.

Onderzoeksproduct en/of interventie

Patients will be treated with a combination of clofarabine, liposomal daunorubicina nd cytarabine. Clofarabine is the IMP in this study.

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. 2nd relapse of AML;

2. Refractory AML in 1st relapse (defined as ≥ 20% blasts in the bone marrow after the 1st course of re-induction therapy according to the AML 2001/01 protocol);

3. 1st early relapse (relapse within one year from initial diagnosis) of AML (only when the Relapsed AML 2001/01 study is closed);

4. ≤ 18 years old at initial diagnosis;

5. Lansky play score > 60; or Karnofsky performance status > 60;

6. Life expectancy 6 weeks;

7. Calculated creatinine clearance ≥ 90 ml/min/1.73m2 as calculated by the Schwartz formula for estimated glomerular filtration rate (GFR) where GFR (ml/min/1.73 m2) = k*Height (cm)/serum creatinine (mg/dl). k is a proportionality constant which varies with age and is a function of urinary creatinine excretion per unit of body size; 0.45 up to 12 months of age; 0.55 children and adolescent girls; and 0.70 adolescent boys;

8. Liver function:

A. Serum bilirubin ≤1.5 × upper limit of normal (ULN);

B. Aspartate transaminase (AST)/alanine transaminase (ALT) <=2.5 × ULN;

C. Alkaline phosphatase <= 2.5 × ULN.

9. Able to comply with scheduled follow-up and with management of toxicity;

10. For female patients with childbearing potential, a negative test for pregnancy is to be considered before entry on study;

11. Male and female patients must use an effective contraceptive method during the study and for a minimum of 6 months after study treatment;

12. Written informed consent from patients or from parents or legal guardians for minor patients, according to local law and regulations.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Isolated extramedullary relapse, including isolated CNS-relapse;

2. Symptomatic CNS leukemia in case of combined relapse;

3. Relapsed/refractory acute promyelocytic leukemia (APL);

4. Relapsed/refractory myeloid leukemia of Down Syndrome (ML DS);

5. Other serious illnesses or medical conditions;

6. Current uncontrolled infection;

7. Evidence of cardiac dysfunction (shortening fraction below 28%);

8. Pregnant or lactating patients;

9. 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);

10. History of prior veno-occlusive disease (VOD);

11. Hypersensitivity to cytarabine, clofarabine or liposomal daunorubicin;

12. 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;

13. GCSF will not be used for priming and no routine GCSF support is allowed during the 1st course, except for life-threatening infections;

14. In case of non-symptomatic CNS-involvement, intrathecal therapy is allowed according to investigator's discretion. It is not allowed to give intrathecal therapy prior to treatment with

clofarabine, as we do not know if this can be done without safety concerns. Hence, this should be delayed to day +7 of treatment, which will allow us to assess the CSF penetration of clofarabine (clofarabine CSF levels and early response). In case of neurotoxicity experienced during the IV treatment, the intrathecal may need to be further delayed.

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 gestopt
(Verwachte) startdatum:	01-08-2009
Aantal proefpersonen:	28
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	25-06-2009
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	NL1770
NTR-old	NTR1880
Ander register	I-BFM 2009/02 : ITCC020
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A