Development and introduction of a pediatric liquid formulation of 6-mercaptopurine for treatment of leukemia.

Gepubliceerd: 18-01-2009 Laatst bijgewerkt: 13-12-2022

6MP treatment in pediatric ALL patients can be improved by developing a pediatric oral drinking solution of 6MP, assessing its bioequivalence, and -when successful- introducing the new formulation nationwide.

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

Samenvatting

ID

NL-OMON20904

Bron
NTR

Verkorte titel
6MP formulation

Aandoening

acute lymphoblastic leukemia in pediatric patients

acute lymfatische leukemie bij kinderen

Ondersteuning

Primaire sponsor: Erasmus MC
Hospital Pharmacy and Pediatric Oncology
Overige ondersteuning: Stichting Kinderen Kankervrij, Nederland

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Blood levels of the metabolites of 6MP will be analyzed after administration of the two different formulations, in order to establish the bio-equivalence of the liquid formulation compared to the capsules.

Toelichting onderzoek

Achtergrond van het onderzoek

Background:
Patients with acute lymphoblastic leukemia (ALL) are currently treated in the Netherlands according to the Dutch Childhood Oncology Group (DCOG) ALL10 protocol, in which the oral cytotoxic drug 6-mercaptopurine (6MP) is administered daily, for a period between one and two years. Because of the lack of a commercially available pediatric formulation of 6MP, 6MP needs to be prepared as capsules containing the specific dosage needed for each patient by community pharmacies. Every 2 weeks the dosage of 6MP is adapted according to the leukocyte count. Since most pharmacies are not equipped to prepare capsules of cytotoxic compounds such as 6MP, the availability (within an acceptable time-window) of 6MP in the correct dosage, after discharge of the patient and after every dosage adaptation, is problematic and may lead to inadequate patient care. Moreover, in order to prepare a drinking solution for younger children, the parents have to dissolve the capsules at home with water before administration. This may lead to unwanted drug exposure of the parents, and may also increase the risk for errors in dosing or administration.
The aim of this study is to improve 6MP treatment in pediatric leukemia patients, by developing and licensing a pediatric liquid formulation of 6MP, assessing its stability and bioequivalence, and ensuring a nationwide introduction of the new formulation.

Study design:
A crossover open label study will be performed, with 20 patients from different age groups (infants 1 month- 2 years of age; young children 2-6 years; school children 6-12 years; adolescents 12-18 years). Patients will receive 4 weeks treatment with capsules, followed by 4 weeks treatment with liquid formulation, or vice versa. Patients will participate in the study during a regular treatment phase with 6MP, according to the ALL-10 or Interfant protocol.

Endpoints:
Bioequivalence will be assessed by determining blood levels of the active metabolites of 6MP in red blood cells. Two-weekly leukocyte counts will be performed to monitor hematological toxicity. Compliance and acceptance of the different formulations by children and parents will

be assessed.

Doel van het onderzoek

6MP treatment in pediatric ALL patients can be improved by developing a pediatric oral drinking solution of 6MP, assessing its bioequivalence, and -when successful- introducing the new formulation nationwide.

Onderzoeksopzet

For each participant, the study period is 8 weeks, with a cross-over to a different formulation after 4 weeks.

Onderzoeksproduct en/of interventie

Patients will be randomized to receive 4 weeks 50 mg/m2 /day 6MP as a capsule and subsequently 4 weeks the same dosage of 6MP as a liquid drinking solution, or vice versa. Patients will participate in the study during a regular treatment phase with 6MP, according to the ALL-10 or Interfant protocol. Bioequivalence will be assessed by determining blood levels of the active metabolites of 6MP in red blood cells. Two-weekly leukocyte counts will be performed to monitor hematological toxicity. Compliance and acceptance of the different formulations by children and parents will be assessed.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Histologically or cytologically confirmed diagnosis of ALL;

2. Inclusion in DCOG ALL-10 or Interfant-06 protocol;

3. Recovered from acute side-effects of previous treatment blocks;

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

5. Normal liver function defined as less than or equal to NCI-CTG grade 1 (max 2.5 x ULN for transaminases and bilirubin);

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

7. Age 1 month-18 years;

8. Available venous access port;

9. 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. Patient refusal or parent refusal;

2. Patients with pre-existing liver disease;

3. Other serious illnesses or medical conditions.

Onderzoeksopzet

Opzet

Type: Interventie onderzoek

Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	Geneesmiddel

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	15-02-2009
Aantal proefpersonen:	20
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	18-01-2009
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	NL1555
NTR-old	NTR1633
Ander register	EudraCT : 2008-000424-86
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten

ALL-10 study protocol, the Dutch Childhood Oncology Group. Principal investigator: Prof.dr. Rob Pieters.

INTERFANT-06. International collaborative treatment protocol for infants under one year of age with acute lymphoblastic or biphenotypic leukemia. Dutch Childhood Oncology Group, Principal investigator: Prof.dr. Rob Pieters.

B.A. Bell et al. A comparison of red blood cell thiopurine metabolites in children with acute lymphoblastic leukemia who received oral mercaptopurine twice daily or once daily: A Pediatric Oncology Group study (now The Children's Oncology Group). Pediatr Blood Cancer 2004;43(2):105-9

F Innocenti et al. Variable correlation between 6-mercaptopurine metabolites in erythrocytes and haematological toxicity; implications for drug monitoring in children with acute lymphoblastic leukemia. Ther Drug Monit 2000; 22(4): 375-382.

Balis FM et al. Pharmacokinetics and pharmacodynamics of oral methotrexate and mercaptopurine in children with lower risk acute lymphoblastic leukemia; a joint children’s cancer group and pediatric oncology branch study, Blood 1998 (92); 3569-3577

Chrzanowska M, Kolecki P, Duczmal-Cichocka B, Fiet J. Metabolites of mercaptopurine in red blood cells: a relationship between 6-thioguanine nucleotides and 6-methylmercaptopurine metabolite concentrations in children with lymphoblastic leukemia Eur J Pharm Sci.1999; 8(4):329-34.

Lennard L, Keen D, Lilleyman JS. Oral 6-mercaptopurine in childhood leukemia: parent drug pharmacokinetics and active metabolite concentrations. Clin Pharmacol Ther. 198640(3):287-92.

EMEA Note for guidance on the investigation of bioequivalence and bioequivalence (2001 cpmp/ewp/qwp/1401/98)