Phase 0 clinical trial to determine capecitabine exposure in patients that have administered a new controlled release tablet of capecitabine, named ModraCape001.

No registrations found.

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

Summary

ID

NL-OMON21513

Source
NTR

Health condition

Patients with cancer who might benefit from treatment with capecitabine, e.g. colon, breast, pancreatic and gastric cancer, ACUP.

Sponsors and support

Primary sponsor: The Netherlands Cancer Institute
Source(s) of monetary or material Support: The Netherlands Cancer Institute

Intervention

Outcome measures

Primary outcome

To determine the plasma pharmacokinetics of capecitabine after intake of different

formulations of ModraCape and after intake of Xeloda®.

Secondary outcome

1. To determine the plasma AUC of capecitabine and its metabolites 5-dFCR, 5-dFUR and 5-FU after administration of different ModraCape formulations and Xeloda;

2. To determine the intracellular pharmacokinetics of 5-FU nucleotides after administration of different formulations of ModraCape or Xeloda;

3. To determine dihydropyrimidine dehydrogenase (DPD) enzyme activity in peripheral blood mononuclear cells (PBMCs);

4. To determine thymidylate synthase (TS) enzyme activity in peripheral blood mononuclear cells (PBMCs);

5. To determine the preliminary safety and tolerability profile of different formulations of ModraCape.

Study description

Background summary

In this study, the pharmacokinetics of different formulations of ModraCape will be tested and compared with the pharmacokinetics of Xeloda®. The hypothesis is to identify a formulation of ModraCape that will release capecitabine in vivo over a time-period of about 18 hours. Testing in humans of several formulations is necessary due to the lack of a good pre-clinical model able to predict the Pharmacokinetics of ModraCape in humans.

Study objective

The objective is to identify a formulation of ModraCape001 that will release capecitabine in vivo over a time-period of about 18 hours. We hypothesize that prolonged exposure, without a high peak exposure to capecitabine, improves the benefit/risk ratio of capecitabine.

Study design

Patients will be hospitalized for three days. At the first day they will receive one dose of 1000 mg Xeloda® at approximately 09:00 h. After intake at blood samples will be collected up to 12 hours after intake to determine PK and PD. At day 2 patients will receive one dose of 1000 mg ModraCape at approximately 9:00 h and blood sample collection will be done for the next 33 hours postdose. A follow-up visit after one week will be planned for safety reasons.

Intervention

This is a proof of concept and pharmacological phase 0 crossover study whereby the new oral formulation of capecitabine, ModraCape001, will be investigated. The primary endpoint is to determine the pharmacokinetic profile of ModraCape001 and to compare this profile with the pharmacokinetic properties of Xeloda®. Patients will be hospitalized for three days. At the first day they will receive one dose of 1000 mg Xeloda® at approximately 09:00 h. After intake blood samples will be collected up to 12 hours after intake to determine pharmacokinetics (PK) and pharmacodynamics (PD). At day 2 patients will receive one dose of 1000 mg of different formulations of ModraCape and blood sample collection will be done at similar time points for the next 33 hours postdose. After the final blood sample is collected the patient will be released from the hospital. A follow-up visit after one week will be planned for safety reasons. If no further follow-up is needed for safety reasons the patient will be declared off-study. Further treatment is determined in the best interest of the patient in consultation with the treating physician. Proof of principle is achieved when the mean AUC of capecitabine after intake of ModraCape is ≥ 50% of the mean AUC of capecitabine after intake of the same dose of Xeloda® and if the mean AUC of capecitabine up to 2 hours (AUC0-2) with ModraCape is <50 % of that observed with Xeloda®. The latter iwould indiate that ModraCape is indeed a slow release formulation compared to Xeloda®.

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Eligibility criteria

Inclusion criteria

1. Histological or cytological proof of cancer;

2. Patient who might benefit from treatment with capecitabine, e.g. colon, breast, pancreatic and gastric cancer, ACUP;

3. Age: 18 years or older;

4. WHO performance status of 0, 1 or 2;

5. Able and willing to give written informed consent;

6. Able and willing to undergo blood sample collection for pharmacokinetic (PK) measurements and biomarker analysis;

7. ife expectancy is at least 3 months allowing adequate follow up;

8. Minimal acceptable safety laboratory values:

A. ANC of at least 1.5 x 109 /L;

B. Platelet count of at least 100 x 109 /L;

C. Hemoglobin of at least 6.5 mmol/L;

D. Hepatic function as defined by serum bilirubin not higher than 1.5 x ULN, ALAT and ASAT not higher than 3.0 x ULN (not higher than 5 x ULN in case of liver metastases);

E. Renal function as defined by serum creatinine not higher than 1.5 x ULN or creatinine clearance at least 50 ml/min (by Cockcroft-Gault formula).

9. No radio- or chemotherapy within 3 weeks of receiving first dose of study medication (palliative limited radiation of 1 x 8 Gy for pain reduction is allowed);

10. Able and willing to swallow oral medication;

11. Negative pregnancy test (urine/serum) for female patients with childbearing potential.

Exclusion criteria

1. Dihydropyrimidine dehydrogenase (DPD) deficiency as assessed on the basis of DPYD mutation analysis;

2. Women who are pregnant or breast feeding;

3. Both men and women enrolled in this trial must agree to use a reliable contraceptive method throughout the study (adequate contraceptive methods are: condom, sterilization, other barrier contraceptive measures preferably in combination with condoms);

4. Bowel obstructions or motility disorders that may influence the absorption of drugs;

5. Pre-existing neuropathy > grade 1;

6. Unresolved (> grade 1) toxicities (except alopecia) of previous chemotherapy;

7. Patients with known alcoholism, drug addiction and/or psychotic disorders in the history that are not suitable for adequate follow up;

8. The use of any drug or complementary alternative medicine that might interfere with the biotransformation of capecitabine and/or 5FU, like CYP2C9 substrates with narrow therapeutic windows (e.g., vitamin K antagonizing anticoagulants [acenocoumarol, phenprocoumon, warfarin], phenytoin), allopurinol, folic acid, folinic acid, interferon alpha, metronidazol, sorivudine (and analogues), aluminium hydroxide and magnesium hydroxide;

9. Current participation or previous participation in a study with an investigational compound, or chemo- and/or radiotherapy within 21 days of receiving first dose of study medication. (Palliative limited radiation of 1 x 8 Gy for pain reduction is allowed);

10. Prior stem cell or bone marrow transplant;

11. Known hypersensitivity to the components of the study drug or its analogs;

12. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients;

13. Patients with a known history of hepatitis B or C;

14. Symptomatic cerebral or leptomeningeal metastases;

15. Neurologic disease that may render a patient at increased risk for peripheral or central neurotoxicity;

16. Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-12-2011
Enrollment:	30
Type:	Anticipated

Ethics review

Positive opinion

Date:	03-10-2012
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	NL3515

Register	ID
NTR-old	NTR3647
Other	:
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A