Pharmacological study of chronomodulated capecitabine therapy

No registrations found.

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

Summary

ID

NL-OMON24089

Source
Nationaal Trial Register

Health condition

cancer, capecitabine, phase I, chronotherapy, biomarker, pharmacology, kanker, chronotherapie,
fase I

Sponsors and support

Primary sponsor: Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital
Source(s) of monetary or material Support: Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital

Intervention

Outcome measures

Primary outcome

To determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs) and recommended dose (RD) of continuous and intermittent chronomodulated capecitabine.

Secondary outcome

The plasma pharmacokinetics of capecitabine and its metabolites 5-dFCR, 5-dFUR, 5-FU and FBAL;

The inter- and intra-patient variability in plasma pharmacokinetics;

Baseline and circadian dihydropyrimidine dehydrogenase (DPD) activity in peripheral blood mononuclear cells (PBMCs) and
in plasma by means of the dihydrouracil (UH2) / uracil (U) ratio;

Baseline and circadian thymidylate synthase (TS) activity in PBMCs;

Baseline thymidine phosphorylase (TP) activity in PBMCs;

The description of pharmacokinetic/pharmacodynamic (PK/PD) relationships;

The preliminary antitumor activity of chronomodulated capecitabine;

Associations of polymorphisms in DPYD or TYMS with DPD or TS enzyme activity in PBMCs and clinical response;

Intracellular pharmacokinetics of 5-FU nucleotides in PBMCs.

Study description

Background summary

Capecitabine is a widely used oral prodrug of 5-fluorouracil (5-FU). Enzymatical conversion of capecitabine subsequently by carboxyl esterase (CES), cytidine deaminase (CDA) and thymidine phophorylase (TP) is warranted for the formation of 5-FU. However, the clinical application of capecitabine is limited by treatment failure and poorly predictable severe toxicity (especially diarrhea and palmar-plantar erythrodysesthesia (PPE)). Treatment safety and efficacy may be improved by synchronization of capecitabine therapy to the circadian rhythm of the 5-FU degrading enzyme dihydropyrimidine dehydrogenase (DPD) and its drug target thymidylate synthase (TS). Approximately 80% of 5-FU is metabolized by DPD. Earlier studies, including an observational study performed by our research group, showed that DPD activity fluctuates over the twenty-four hours of the day. This so called circadian rhythm of DPD is characterized by low metabolic capacity during day-time and peak metabolic capacity during the night. Nocturnal DPD activity is approximately 60% higher compared to DPD activity in the afternoon.
Consequently, metabolism of 5-FU is most likely increased during the night because of high DPD activity. Besides circadian activity of DPD the enzyme thymidylate synthase (TS) also shows circadian activity. The enzyme TS displays trough activity during the night. Exposure to 5-FU when TS activity is low has been associated with improved 5-FU tolerability. Circadian rhythms of DPD and TS presumably affect capecitabine treatment pharmacokinetics, safety

and tolerability. Safety and the maximum tolerated dose (MTD) for Xeloda® have been determined in earlier phase I trials for continuous and intermittent (day 1-14 of a 21-day course) BID treatment schedules with Xeloda®. Major limitations of these studies were that circadian rhythms in 5-FU metabolism were not taken into account. Chronomodulated capecitabine therapy, indicating that capecitabine therapy is synchronized to circadian rhythms of DPD and TS, might be advantageous for Xeloda® BID treatment. Therefore, we aim to determine the feasibility of chronomodulated capecitabine in a pharmacological phase I clinical study. A new capecitabine dosing schedule is developed by population modeling of capecitabine pharmacokinetics and DPD activity. Capecitabine will be administered continuously on day 1-21 (arm A) and intermittently on day 1-14 (arm B) of 21-day BID dosing schedules. For both study arms, the morning dose will be administered at 9:00 hours (h) and the late evening dose at 24:00 h. Chronomodulation will be obtained by using a relatively high evening dose of capecitabine.

Country of recruitment: The Netherlands

Study objective

Circadian rhythms of dihydropyrimidine dehydrogenase and thymidylate synthase might affect capecitabine tolerability. It is expected that high dose capecitabine during the night is better tolerated because of these circadian rhythms.

Study design

Screening: PD sampling for DPD, TS and TP activity;

Day 7 and 8: PK sampling capecitabine (metabolites), PD sampling for DPD, TS and TP activity;

End of treatment: PD sampling for DPD, TS and TP activity.

Safety measurements will be performed every week of the first treatment course, and every first day of subsequent treatment courses.

Intervention

Capecitabine will be administered exactly at 9:00 h and 24:00 h on day 1-21 (arm A) and 1-14 (arm B) of a 21-day treatment schedule. To obtain chronomodulation the ratio of the morning to the evening dose will be maintained at 3(morning dose):5(evening dose).

Contacts

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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

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 during day-time and during the night for pharmacokinetic (PK) measurements and pharmacodynamic (PD) analysis;

7. Life expectancy >3 months allowing adequate follow up;

8. Minimal acceptable safety laboratory values

a. ANC of > 1.5 x 109 /L;

b. Platelet count of > 100 x 109 /L;

c. Hemoglobin > 6.5 mmol/L;

d. Hepatic function as defined by serum bilirubin 1.5 x ULN, ALAT and ASAT < 3.0 x ULN (< 5 x ULN in case of liver metastases);

e. Renal function as defined by serum creatinine ¡Ü1.5 x ULN or creatinine clearance > 60 ml/min (by Cockcroft-Gault formula).

9. No radio- or chemotherapy within 3 weeks of receiving first dose of study medication (palliative limited radiation 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 IVS14+1G>A (DPYD*2A) and 2846A>T 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 can not be administered in the morning and evening/night: the use of aluminium hydroxide and magnesium hydroxide is not an exclusion criterion when administered in the afternoon between 12:00 - 18:00 h;

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 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. 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 capecitabine according to this protocol or puts the patient at high risk for treatment-related complications.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-06-2014
Enrollment:	42
Type:	Anticipated

Ethics review

Positive opinion
Date: 30-06-2014
Application type: First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 40756
Bron: ToetsingOnline
Titel:

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
NTR-new	NL4135
NTR-old	NTR4639
CCMO	NL48425.031.14
OMON	NL-OMON40756

Study results