Development and clinical activity of low dose metronomic chemotherapy with oral paclitaxel

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We will develop a bi-daily low-dose metronomic treatment schedule with paclitaxel in a convenient oral formulation and test whether this therapy has significant anti-angiogenic and anti-tumor activity.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON44720

Source
ToetsingOnline

Brief title
N10MOP

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, malignancy

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Nederlands Kanker Instituut - Antoni van

Leeuwenhoek Ziekenhuis

Intervention

Keyword: LDM therapy, oral, paclitaxel, ritonavir

Outcome measures

Primary outcome

To determine the safety and feasibility of LDM bi-daily oral paclitaxel (as ModraPac005 tablets) in combination with boosting agent ritonavir.

Secondary outcome

• To determine the optimal biological recommended dose (OBDRD) of bi-daily oral paclitaxel in combination with ritonavir.

• To determine the maximal tolerated dose (MTD, or maximal safe dose) to assess the safety range.

• Pharmacokinetics of paclitaxel and ritonavir in this schedule.

• To preliminary asses the efficacy of LDM treatment, measured by PFS, response rates, duration of response and duration of disease control.

• To establish the effect of functional genetic polymorphisms in six genes (SLCO1B3, ABCB1, ABCC2, CYP3A4, CYP3A5 and CYP2C8, C1236T (for MDR1) and CYP3A4*1B, on the pharmacokinetics of oral paclitaxel and ritonavir.

• To determine the effect of a high-fat meal on the exposure of ModraPac005/r

Study description

Background summary

In classical dose-intensive oncolytic therapy it is believed that the highest tolerable dose-intensity (MTD) will result in the highest anti-tumor activity.

An alternative is *low dose metronomic (LDM) chemotherapy*, i.e. chronic administration of oncolytic drugs at relatively low, non-toxic doses on a frequent administration schedule with no drug-free breaks. Unlike dose-intensive therapy directly aimed at tumor cell kill, the main target is dividing endothelial cells of the growing vasculature of a tumor. Administration of dose-intensive chemotherapy may not lead to optimal anti-tumor activity, but often exposes patients unnecessarily to severe side-effects. In fact, it will probably thwart the anti-vasculogenetic capacity of the therapy.

Based on preclinical data, the taxane paclitaxel is considered to be an ideal drug to use for the concept of metronomic therapy, if repeated oral dosing would be possible. We are the first to have successfully developed an oral treatment strategy for paclitaxel, for which we recently developed a novel capsule formulation of paclitaxel. In combination with the oral boosting agent ritonavir high apparent bioavailability of oral paclitaxel is achieved when given as a drinking solution, or in a capsule/tablet formulation. This strategy has turned out to be safe and active upon prolonged once weekly BID dosing of patients with various types of solid tumors at MTD. A capsule preparation has thus far been used. A novel tablet formulation (ModraPac005 tablet) has been produced, a tablet has advantages, since these are better produceble and therefore easier to incorporate in a possible fase II study. The novel tablet formulation will be implemented in the dose expansionfase when available.

Study objective

We will develop a bi-daily low-dose metronomic treatment schedule with paclitaxel in a convenient oral formulation and test whether this therapy has significant anti-angiogenic and anti-tumor activity.

Study design

Dose-escalation of paclitaxel
The OBD of paclitaxel in combination with ritonavir will be determined by dose escalation. Three patients will be assigned to each dose level. On a predefined day the patient will start receiving oral paclitaxel BID, dosed according to the escalation schedule and 100 mg ritonavir (see *dose escalation and study treatment*). This regime will be continued until progressive disease or until adverse events, which require dose modifications or discontinuation of therapy, are observed. Three weeks will be seen as one course. Weekly physical examination, blood hematology and blood chemistry parameters will guide the safety of the treatment. If one patient of the first three at a defined dose-level experiences dose limiting toxicity (DLT), the number of patients treated at this dose level will be expanded to a maximum of six. The dose escalation will continue if none of the additional patients experiences a DLT. The safety range (*Therapeutic Window*) of this schedule will be determined by

assessing the MTD, defined as the highest safe bi-daily dose of oral paclitaxel using classical clinical and laboratory endpoints (the dose-level at which maximally one out of six patients develops a DLT).

Expansion phase
At the dose-level of the expected OBD the number of patients treated at this dose will be expanded to a maximum of twelve. In this phase the effect if food intake on the pharmacokinetic results will be analysed. If the pharmacokinetic results are not affected by the intake of food, then the treatment of future patients can be more convenient by removal of the obligated fasted state around the bidaily intake of the tablets.

Intervention

Only patients who fulfil all in- and exclusion criteria can enroll in this study and can receive this therapy.

Study burden and risks

Patients participating will be hospitalized during the first day of treatment. Blood will be drawn for pharmacokinetic research, hematology, and serum chemistry (see *Pharmacokinetics*). The patient will have to visit the hospital once every week.
Patients are at risk for paclitaxel related side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients with histological or cytological proof of cancer who might benefit from treatment with paclitaxel
- Patients for whom no standard therapy of proven benefit exist;- Age =/> 18 years;- Able and willing to give written informed consent;- Able and willing to undergo blood sampling for pharmacokinetics and pharmacodynamics;- Life expectancy =/> 3 months allowing adequate follow up of toxicity evaluation and anti-tumor activity;- Minimal acceptable safety laboratory values;a. ANC of =/> 1.5 x 109 /L;b. Platelet count of =/> 100 x 109 /L;c. Hepatic function as defined by serum bilirubin </= 1.5 x ULN, ALAT and ASAT </= 2.5 x ULN;d. Renal function as defined by serum creatinine </= 1.5 x ULN or creatinine clearance =/> 50 ml/min (by;Cockcroft-Gault formula).;- WHO performance status of </= 2;- No radio- or chemotherapy within the last 4 weeks prior to study entry ;- Able and willing to swallow oral medication;for expansion phase: able and willing to consume a high-fat meal

Exclusion criteria

1. Patients with known alcoholism, drug addiction, psychotic disorders in the history and/or other reasons, for which they are not amenable for adequate follow up.;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. Concomitant use of MDR and CYP3A modulating drugs such as Ca+ entry blockers (verapamil, dihydropyridines), cyclosporine, (non) nucleoside analoga, St. Johns worth, macrolide antibiotics as erythromycin and clarithromycin, quinidine, quinine, tamoxifen, megestrol, grapefruit juice, concomitant use of HIV medications or other protease inhibitors. ;5. Uncontrolled infectious disease or known HIV-1 or HIV-2 type patients;6. Unresolved (>grade 1) toxicities of previous chemotherapy, excluding alopecia;7. Known allergic reaction against contrast agents;8. Bowel obstructions or motility disorders that may influence the absorption of drugs;9. Neurologic disease that may render a patient at increased risk for peripheral or central neurotoxicity;10. Pre-existing neuropathy greater than CTC grade 1;11. Symptomatic cerebral or leptomeningeal metastases;12. 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

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-08-2011
Enrollment:	56
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	paclitaxel
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Norvir
Generic name:	Ritanovir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-07-2010

Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-09-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-08-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-03-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-10-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-10-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	16-04-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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
EudraCT	EUCTR2010-021525-13-NL
CCMO	NL33122.031.10