Measurement of tumor kinase inhibitor concentrations using PET imaging in patients with advanced solid malignancies

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

Summary

ID

NL-OMON40107

Source
ToetsingOnline

Brief title
PET imaging of kinase inhibitors

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer; metastasized malignancy

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: bedrijf,Hoffmann-La Roche

Intervention

Keyword: advanced solid malignancy, intratumoral concentration, kinase inhibitor, PET imaging

Outcome measures

Primary outcome

1) Tumor uptake of [11C]sorafenib cq [11C]erlotinib before and on treatment (%

injected dose and activity concentration in tumor lesions)

2) Image derived imput function of [11C]sorafenib cq [11C]erlotinib before and

on treatment (% injected dose and activity concentration in large bloodvessels)

3) Pharmacokinetics [11C]sorafenib cq [11C]erlotinib before and on treatment

(plasma and whole blood; % injected dose and activity concentration/g)

4)On treatment tumor concentration of sorafenib cq erlotinib.

Secondary outcome

5) Tumor perfusion as measured with [15O]water before and on treatment (%

injected dose and activity concentration in tumor lesions)

6) Image derived imput function of [15O]water before and on treatment (%

injected dose and activity concentration in large bloodvessels)

7) Kinase activity in tumor biopsies before and after treatment with sorafenib

cq erlotinib.

8) Phosphoproteomics analysisin tumor biopsies before and after treatment with

sorafenib cq erlotinib.

Study description

Background summary

Multiple agents targeting specific signaling proteins important for tumor growth and angiogenesis, including (tyrosine) kinase inhibitors and monoclonal antibodies, have been developed and have reached clinical approval. In general, however, these targeted agents induce a response only in a subgroup of cancer patients, while all are exposed to potential toxic therapies. Prior to treatment, it is unknown which patients will respond and why kinase inhibitors are only effective in some, but not all, patients. Clearly, there is a need for a non-invasive in vivo technique to identify those patients who may benefit from treatment with a specific drug.
Positron emission tomography (PET) is a non-invasive technique that enables quantitative measurements of molecular pathways and interactions with picomolar sensitivity and, as such, it has the potential to fulfill the need mentioned above. We expect that response to kinase inhibitors is dependent on achieving active drug levels in tumor tissue. Currently, intratumoral kinase inhibitor levels are being investigated at our institution (ICK study). However, these measurements require fresh tumor biopsies. We hypothesize that radiolabeled kinase inhibitor PET imaging can quantify concentrations of labeled drug in tumor lesions, thereby avoiding burdensome biopsies in the future.

Study objective

The main objective of this study is to determine whether tumor concentrations of kinase inhibitors at pharmacological active doses can be predicted from PET studies using tracer amounts (microdosing) of corresponding radiolabeled kinase inhibitors. This objective includes the development and validation of pharmacokinetic models for radiolabeled kinase inhibitors as well as validation of the microdosing concept for kinase inhibitors.
The secondary objectives include exploration whether kinase inhibitor kinetics depend on perfusion (as measured by [15O]water PET) or size (as measured by diagnostic CT/MRI) of tumor lesions and to investigate (in)activation of key pathways targeted by the specific kinase inhibitor.

Study design

Single center, non-randomized, interventional proof of concept study.

Intervention

Patients will be treated with the kinase inhibitor according to standard treatment. Patients with an indication to start the investigated kinase inhibitor (i.e. sorafenib and erlotinib in this study, with the aim to

investigate others in future studies, such as pazopanib and axitinib among others) will have a [11C] kinase inhibitor PET-CT and [15O]water PET-CT before and after two weeks of treatment. Tumor biopsies will be performed before and during therapy (category 1). Patients already on treatment with the investigated kinase inhibitor and who have stable disease for at least 4 months, a partial or a complete response will only have a [11C] kinase inhibitor PET-CT and [15O]water PET-CT during treatment and one tumor biopsy performed during treatment (category 2).

Study burden and risks

Enrolment in this study will require two tumor biopsies, 2x [11C] kinase inhibitor PET-CT, 2x [15O]water PET-CT and arterial blood sampling for patients with an indication to start the investigated kinase inhibitor (category 1). Patients already on treatment with the invastigated kinase inhibitor with stable disease for at least 4 months, a partial response or complete response will require one tumor biopsy, 1x [11C] kinase inhibitor PET-CT, 1x [15O]water PET-CT and arterial blood sampling (category 2). The biopsies may cause physical discomfort. During therapy, follow-up will include standard laboratory analysis as well as regular visits to the outpatient clinic. The radiation exposure is acceptable. Patients treated with a kinase inhibitor as standard therapy may benefit from disease regression or stabilization as it has proven clinical benefit in the patient population under investigation. The results of this kinase inhibitor PET imaging study will be strongly supportive for the development of non-invasive, personalized treatment strategies thereby avoiding cumbersome tumor biopsies and unwanted exposure to potentially toxic drugs.

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 must have a histologically confirmed diagnosis of an advanced or metastatic solid malignancy. ;* A. Patients must have confirmed radiological or clinical progressive disease with a standard indication to start sorafenib or erlotinib (category 1).
OR B. Patients must have stable disease for at least 4 months, a partial response or a complete response established with RECIST version 1.1 within 21 days before the radiolabeled kinase inhibitor scan if they are already on treatment with sorafenib or erlotinib (category 2).;* Patients must have at least one measurable tumor lesion outside the liver.;* Indication for standard use of palliative systemic treatment, with sorafenib or erlotinib.;* Age * 18 years. ;* ECOG Performance Status * 2.;* Life expectancy of at least 12 weeks.;* Patients should be able to swallow oral medication.;* Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:;o Hemoglobin * 6.0 mmol/L;o Absolute neutrophil count (ANC) * 1,5 x 10*9/L ;o Platelet count * 100 x 10*9/L;o Total bilirubin * 2 times the upper limit of normal (ULN);o ALT and AST* 2.5 x ULN; * 5x ULN in case of liver metastases, except for patients with hepatocellular carcinoma, than Child Pugh classification A-B.;o Alkaline phosphatase < 4 x ULN; * 5x ULN in case of liver metastases, except for patients with hepatocellular carcinoma, than Child Pugh classification A-B.;o Serum creatinine eGFR * 50 mL/min. ;o PT-INR/PTT < 1.5 x ULN, unless coumarin derivatives are used.;o Activated partial thromboplastin time < 1.25 x ULN (therapeutic anticoagulation therapy is allowed, if this treatment can be interrupted for a biopsy as judged by the treating physician).

Exclusion criteria

* Concurrent treatment with other anticancer agents or experimental drugs.;* History of cardiac disease: ;o Congestive heart failure >NYHA class 2. ;o Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening).;* Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted). ;* Uncontrolled

hypertension. Blood pressure must be *160/95 mmHg at the time of screening on a stable antihypertensive regimen. Blood pressure must be stable on at least 2 separate measurements.;* Uncontrolled infections (> grade 2 NCI-CTC version 4.0).;* Subjects with serious non-healing wound, ulcer, or bone fracture.;* Patients with thromboembolic events within 3 months prior to study inclusion.;* Significant skin condition interfering with treatment;* Patients undergoing renal dialysis.;* Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment. Both men and women enrolled in this trial must agree to use adequate barrier birth control measures (e.g., cervical cap, condom, or diaphragm) during the course of the trial. Oral birth control methods alone will not be considered adequate on this study, because of the potential pharmacokinetic interaction between study drug and oral contraceptives. Concomitant use of oral and barrier contraceptives is advised. Contraception is necessary for at least 6 months after receiving the study kinase inhibitor.;* Concomitant use of dexamethasone, anti-convulsants and anti-arrhythmic drugs other than digoxin or beta blockers.;* Major surgery within 28 days prior to start of treatment.;* Medical, psychological or social conditions that may interfere with the subject*s participation in the study or evaluation of the study results.;* Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-09-2013
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	11C-erlotinib

Generic name:	11C-erlotinib
Product type:	Medicine
Brand name:	11C-sorafenib
Generic name:	11C-sorafenib
Product type:	Medicine
Brand name:	Nexavar
Generic name:	sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tarceva
Generic name:	erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-02-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-004961-42-NL
CCMO	NL42402.029.12