Improving CNS penetration of radiolabeled TKI PET tracers through PgP/BCRP inhibition

Published: 17-03-2014
Last updated: 20-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Observational invasive

Summary

ID

NL-OMON41107

Source
ToetsingOnline

Brief title
M14EEP:Improving CNS uptake of TKI PET tracers through PgP/BCRP inhibition

Condition

- Metastases

Synonym
Prevention and treatment of brain tumors and metastases

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Startgeld Antoni van Leeuwenhoek

Intervention

Keyword: Blood brain barrier, P-glycoprotein, Positron emission tomography, Tyrosine kinase inhibitor

Outcome measures

Primary outcome

The primary parameter of this study is to obtain clinical proof of principle

that the addition of a PgP/BCRP inhibitor increases CNS concentrations of TKIs

by inhibition of drug efflux transporter function in the blood brain barrier.

This will be determined by measuring the difference in estimated influx,

outflux and absolute concentrations of TKI in the brain using dynamic PET

evaluation, with and without the addition of a PgP/BCRP inhibitor.

Secondary outcome

Secondary objectives of this study are the determination of labeling

efficiency, radiochemical purity, sterility, pyrogen and radiation safety of

the newly developed radiolabeled TKI PET tracers.

Study description

Background summary

The development of brain metastases is a common phenomenon in renal cell cancer (RCC), Non Small Cell Lung Cancer (NSCLC), and Her2 positive breast cancer. The median overall survival of patients developing brain metastases is 3 to 6 months. More importantly, brain metastases decrease quality of life by generating symptoms like headache, seizures and mental alterations. We hypothesize that, when TKI treatment is combined with an inhibitor of PgP and BCRP, such as elacridar, TKI concentrations in the central nervous system (CNS) will increase and the development of brain metastases may be prevented.

Animal models suggest that penetration of TKIs through the blood brain barrier (BBB) is limited, due to activity of drug efflux transporters PgP and BCRP. In

PgP knock-out (Abcb1a/1b-/-) mice, TKI drug levels in the CNS can increase 6-fold or more when compared to wild-type mice, as is demonstrated for sunitinib, dasatinib, imatinib, lapatinib, erlotinib and sorafenib. Due to effux of the drug by PgP and BCRP in normal situations, CNS levels of TKI cannot reach levels known to be therapeutic in peripheral organs. In humans sunitinib and lapatinib single agent treatment does not decrease the likelihood of developing brain metastases nor inhibits growth of present brain metastases. In wild-type mice co-administration of the potent PgP/BCRP inhibitor elacridar resulted in significantly increased CNS levels, up to 70-80% of the CNS concentrations established in PgP knock-out mice.

One concern of our novel approach is the possibility of increasing toxicity by increasing plasma levels of the TKI due to drug efflux pump (PgP/BCRP) inhibition. In mice plasma levels of sorafenib were not higher in PgP knock-out mice compared to wild-type mice. However dasatinib and imatinib plasma levels were 1.5 to 2 times higher in PgP knock-out mice.

An open label phase I healthy volunteer study was performed studying the pharmacokinetics of a newly developed elacridar formulation. Doses of 25, 250 and 1000 mg were investigated. The 1000 mg dose level (n = 6) resulted in adequate plasma levels for PgP/BCRP inhibition with minimal side effects.

Recently, a [11C]erlotinib positron emission tomography (PET) tracer has been developed by dr Hendrikse and Dr. Windhorst of the Department of Nuclear Medicine & PET Research of the VU Medical Center and used in human subjects. A complete investigational medicinal product dossier (IMPD) is available. No side effects were seen in these patients at exposure levels adequate for PET imaging. The effort to visualize erlotinib uptake -in this study the aim was to measure uptake in NSCLC tumours and metastases- was successful.

To visualize the penetration of erlotinib through the BBB, [11C]erlotinib PET scans were performed in mice. Time activity curves demonstrated a faster transport of [11C]erlotinib out of the brain in wild type mice compared to mdr1a/1b/Bcrp1 knock out mice. The PET scans showed no [11C]erlotinib uptake in the brain of PgP/BCRP wild-type mice, and clear uptake of [11C]erlotinib in the brain of PgP/BCRP knock-out mice.

Until now all data evaluating whether the addition of a PgP/BCRP inhibitor increases CNS penetration of TKIs has been generated in animal models. This will be the first in human Proof Of Principle (POC) study. Since about 25-50% of NSCLC, RCC and Her2 positive breast cancer patients will develop brain metastases for whom currently effective treatment options are lacking, the need for an effective treatment strategy to prevent and treat brain metastases in these patients is crucial.

Study objective

The primary objective of this study is to obtain clinical proof of principle that the addition of a PgP/BCRP inhibitor increases CNS concentrations of tyrosine kinase inhibitors by inhibition of drug efflux transporter function in the blood brain barrier

Study design

Every patient will undergo two PET scans. For both scans an intravenous bolus of [11C]erlotinib will be administered. For the second scan patients will be instructed to take 1000 mg elacridar orally. This will enable us to measure the uptake of [11C]erlotinib in the brain with and without PgP/BCRP inhibition.

Study burden and risks

Radiation burden 2 PET scans (as with normal PET scans)
Infection or bleeding due to arterial sampling trough the a. radialis catheter.
Infection or bleeding due to venous sampling
Nausea, headache, dizziness, altered taste due to the oral intake of 1000 mg elacridar

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

The study population consists of cancer patients with advanced or metastatic solid tumors for whom no standard therapy is available or for whom a TKI which is a PgP/BCRP substrate is a standard therapeutic option (erlotinib, sunitinib, imatinib, gefitinib, sorafenib, lapatinib, crizotinib, vemurafenib).

Exclusion criteria

Known brain metastases;
Patients who have had previous treatment with central nervous system irradiation;
Treatment with the tyrosine kinase inhibitor used as TKI PET tracer within three half lives before the PET scans;
Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair study compliance;.
Patients are not allowed to use co-medication with PgP or BCRP modulators (including OTC medication).
Patients are also not allowed to use co-medication which are PgP or BCRP substrates as this may lead to increased toxicity.
Known hypersensitivity to erlotinib, elacridar or any excipients used in the formulation of either IMPs.
Known contra-indications for a MRI scan.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-09-2014
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	C11 labeled erlotinib
Generic name:	C11 labeled erlotinib
Product type:	Medicine
Brand name:	Elacridar
Generic name:	Elacridar

Ethics review

Approved WMO

Date:	17-03-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	20-03-2014
Application type:	First submission
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	EUCTR2014-000281-21-NL
CCMO	NL47940.031.14

Study results

Date completed: 31-03-2016

Results posted: 15-05-2017

Actual enrolment: 7

First publication
11-05-2016