Validation of simplified quantitative methods for 3*deoxy-3*-[18F]fluorothymidine Positron Emission Tomography ([18F]FLT PET) in patients with non-small cell lung cancer treated with tyrosine kinase inhibitor (gefitinib of erlotinib).

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Primary objective: association between pharmacokinetic modeling of [18F]FLT PET and simplified measures during treatment with gefitinib in patients with NSCLC to validate the use of simplified measures during treatment with gefitinib of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract neoplasms
Study type	Observational invasive

Summary

ID

NL-OMON36853

Source
ToetsingOnline

Brief title
FLT gefitinib

Condition

- Respiratory tract neoplasms

Synonym
lung cancer, non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: IMI QuIC ConCePT (EU project)

Intervention

Keyword: [18F]FLT PET, NSCLC, Quantification, TKI

Outcome measures

Primary outcome

The study parameters are the results of the simplified measures and the

pharmacokinetic modeling of [18F]FLT PET prior to therapy and during treatment

with gefitinib or erlotinib.

Secondary outcome

Secondary, nonlinear kinetic filtering will be evaluated and perfusion measured

with [15O]H2O PET.

Study description

Background summary

[18F]FLT PET is widely investigated as a proliferation marker in oncology [Bading et.al. J Nucl Med. 2008 Jun;49 Suppl 2:64S-80S]. [18F]FLT follows the salvage pathway of endogenous thymidine in the cell. However, unlike thymidine, [18F]FLT is trapped in the cytosol and is not incorporated into DNA. Published data on [18F]FLT PET are heterogeneous and it is not clear to what extent this relates to different pharmacokinetic characteristics, biological changes, image resolution, or quantification methods. Pharmacokinetic (pk) modelling of PET tracers is the gold standard but it requires arterial blood sampling and dynamic scanning. In case of [18F]FLT, the net uptake rate constant of [18F]FLT, Ki, determined by non-linear regression (NLR) of an irreversible two-tissue compartment model is typically used as the gold standard. Alternatively, kinetic filtering methods have been proposed, requiring

procedures of similar complexity [Gray et.al. Phys Med Biol. 2010 Feb 7;55(3):695-709]. This procedure is not suited for daily clinical practice and it is not suited for whole body acquisitions.
Two simplified methods often are used to (semi-)quantitatively assess [18F]FLT uptake: graphical (Patlak) analysis [Patlak et.al. J Cereb Blood Flow Metab 1985 5:584-590] and standardized uptake values (SUV). Patlak analysis assumes irreversible trapping in tissue, and its accuracy thus depends on the assumption that no significant dephosphorylation occurs within the time course of the study. Both NLR and Patlak measure net uptake of [18F]FLT, taking into account the concentration of tracer in plasma during the course of the study. Only NLR, however, allows for measurements of individual rate constants between compartments and for an implicit correction for blood volume in the tissue of interest. SUV is the ratio of tissue concentration and injected activity at a certain time after administration of the tracer. It does not take tracer kinetics into account, but has the advantage that it is a single scan procedure that does not require plasma data. In daily clinical practice, a static PET scan in whole body mode is the preferred clinical procedure. In this context only SUV is feasible.
For simplified uptake measures to be valid for monitoring response or predicting outcome, their relationship with the more accurate outcome measures of full kinetic analysis must be similar before and after therapy [Hoekstra et.al. Eur J Nucl Med. 2000 Jun;27(6):731-43]. However, systemic therapy might alter the correlations between NLR, Patlak and SUV, as has previously been shown for [18F]fluorodeoxyglucose [Cheebsumon et.a. Eur J Nucl Med Mol Imaging. 2011 May;38(5):832-42]. This could be due to changes in tumour blood flow, blood volume, or plasma clearance of the tracer. The changes are accounted for in full kinetic analysis (NLR), but not in the use of SUV. In untreated cancer patients it has been suggested that SUV is a reasonable alternative for pk modelling [Kenny et.al. Cancer Res 2005 65:10104-10112].

Interpretation of the [18F]FLT signal may be a function of timing of PET during therapy: early during therapy [18F]FLT measurements seem to correlate better with proliferation than late ones [Salskov et.al. Semin Nucl Med. 2007 Nov;37(6):429-39][Benz et.a. Cancer. 2011 Oct 21]. Dynamic scanning at two time-points in the same patient may help to elucidate whether these apparently conflicting findings relate to the applied PET methodology.

Gefitinib and erlotinib are both orally administered tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). Tyrosine kinase inhibitors are of special benefit in patients with NSCLC with an activating EGFR tyrosine kinase mutation. Response rates in a first line setting range from 4-32% in unselected patients and from 55-90% in patients with activating EGFR mutations [Costanzo et.al. J Biomed Biotechnol. 2011;2011:815269].

Study objective

Primary objective: association between pharmacokinetic modeling of [18F]FLT PET

and simplified measures during treatment with gefitinib in patients with NSCLC to validate the use of simplified measures during treatment with gefitinib of erlotinib

Secondary objectives:
1. comparison of baseline kinetic and simplified [18F]FLT measures
2. validation of kinetic filtering methodology
3. impact of perfusion ([15O]H2O) on [18F]FLT uptake prior to therapy and during gefitinib or erlotinib

Study design

Prospective observational multicentre study including 10 eligible patients with NSCLC (tumour size at least 3 cm) will be scanned with [18F]FLT PET on three separate occasions; first within 7 days prior to treatment, subsequently 7 and 28 days after the first dose of gefitinib or erlotinib. Patients will also be scanned with [15O]H2O, prior to the [18F]FLT study, to investigate the impact of perfusion during gefitinib. The dynamic PET scans within the thoracic region will be performed on a PET-CT scanner. During PET, venous samples will be taken at different time points. Dedicated in-house developed software will be used to quantify kinetics. Personal and tumour characteristics will be registered (age, sex, body weight and height, comedication).
Patients will be recruited by the VUmc, UMC St Radboud Nijmegen and local hospitals, Amsterdam, The Netherlands.

Study burden and risks

The venous cannulas will be placed by highly qualified medical doctors of the Department of Nuclear Medicine & PET Research. In spite of this, occasionally these cannulas may cause a hematoma. During the two PET scans a maximum of 180 ml blood is taken.
A PET scan is a regular diagnostic imaging technique. Each study will be conducted in compliance with the radiation safety guidelines of the department. Based on results we obtained from biodistribution studies in rats, whole body radiation after intravenous injection of 300 MBq [18F]FLT is approximately 6.5 mSv, including the low dose CT used for attenuation correction. The whole body radiation of the 300 MBq [15O]H2O will be around 0.3 mSv. Patients will undergo three [18F]FLT PET scans, together with [15O]H2O PET scanning. The total amount of radiation burden will be approximately 20.4 mSv for the entire study. To compare, every person living in the Netherlands receives a natural background radiation dose of 2-2,5 mSv per year.
We are aware that the radiation burden for this study is high, but are of the opinion that this is acceptable for this particular study (with this specific population and high scientific impact). The study population has a median survival of approximately 24-27 months [Morita et.al. Clin Cancer Res. 2009 Jul 1;15(13):4493-8], were the possible hazard of cancer induction by radiation is

after several years. In addition, the patients will very likely receive chemoradiation therapy as part of the best standard of care. The radiation burden from the treatment will be a multitude higher than the radiation dose from the diagnostic work-up and the presently suggested study. In addition, the results of this study will have great clinical benefit in using [18F]FLT PET-CT as drug monitoring tool in the future, improving personalized therapy strategies for cancer patients. We therefore consider the additional radiation burden acceptable and we feel that it outweighs the scientific merit of results that come from the suggested study.

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

* Patient age 18 years or older

* Histological diagnosis of NSCLC
* Active EGFR-TK mutation
* Scheduled for treatment with gefitinib or erlotinib
* Tumour diameter > 3cm (to minimize partial volume effects) within the chest
* Able to remain supine for 90 minutes in the PET-CT scanner
* Written informed consent

Exclusion criteria

* Pregnant or lactating patients
* Metal implants (e.g. pacemakers)
* Body weight > 100 kg

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-11-2012
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	02-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	24-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2013
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
CCMO	NL40585.029.12