[18-F]-Fluordihydrotestosterone PET and [18F]-prostate specific membrane antigen in metastasized castrate resistant prostate cancer

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The objectives of this trial are:1. To define the performance characteristics of FDHT PET in patients with metastasized castrate resistant prostate cancer(mCRPC).(a) To demonstrate the kinetics of displacement of the tracer off of the androgen…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON50549

Source
ToetsingOnline

Brief title
Movember GAP2 project

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
metastasized castrate resistent prostate cancer, Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Movember grant

Intervention

Keyword: FDHT, MRI, PET, Prostate Cancer

Outcome measures

Primary outcome

A definition of the performance characteristics of FDHT PET in patients with mCRPC. Definition of the relationship between FDHT uptake and tumor diffusivity as assessed by whole-body MRI as well as with AR expression, serum androgen levels, androgen levels in biopsy specimens, CTC enumeration, ARV7 presence, and ARV7 nuclear localization. Correlation between PSA and radiological progression free survival time and change in PSMA uptake en MRI from baseline.

Sub-study:

A pharmacokinetic model for [18F]FDHT; an appropriate simplified quantitative method for [18F]FDHT; concordance of DCE-MRI and [15O]-water parameters.

Secondary outcome

Not applicable

Study description

Background summary

The critical pathway that drives prostate cancer growth throughout the natural history of the disease is the androgen receptor (AR), which is present and actively signaling even when the tumor is castration-resistant. The recognition that the AR continues to signal in patients with castration-resistant

metastatic disease is one of the most transformative contemporary biologic discoveries in advanced prostate cancer. The centrality of the AR to tumor progression in metastatic castration-resistant prostate cancer (mCRPC) has resulted in the development of novel AR-targeted therapies, such as androgen biosynthesis inhibitors and pure antiandrogens, that prolong life, reduce pain, and enhance quality of life. Hence, we recognized the clinical need for detecting pharmacodynamic changes caused by treatment with each class of drugs; developing an early indicator of response; and developing predictors of survival.

Means by which AR continues to signal despite castrate levels of serum testosterone could be through AR overexpression, mutation, and ligand-independent activation, among others. [18F]fluorodihydrotestosterone (FDHT) is a positron-emitting radiotracer that provides an innovative way of directly imaging the primary molecular engine of mCRPC. Preliminary studies have demonstrated its safety, feasibility, pharmacokinetic properties, accuracy at identifying prostate tumor, and utility in drug development. Before further efforts to clinically qualify this imaging biomarker are undertaken, however, analytic validation studies in regards to the biomarker*s reproducibility between centers and patients, and correlation with AR expression, must be undertaken. We hypothesize that variability, if present, may be attributed to one or more of the following variables: intrinsic properties of the tracer, tumor AR overexpression, endogenous tumor androgen levels, or tumor perfusion.

Such imaging biomarkers could serve as pharmacodynamic indicators (identifying drug effects), as prognostic indicators (in stratifying patients by risk), and as response indicators (identifying active drugs). This proposal advances a significant body of previous work on development of imaging biomarkers for prostate cancer an This study builds on those efforts, fulfills regulatory requirements for biomarker development, and addresses a significant unmet clinical need. If successful, we will have analytically validated the first imaging biomarker in prostate cancer that directly images the cancer cell by means of its growth engine.

Sub-study:
[18F]Fluorodihydrotestosterone ([18F]FDHT) is a relatively new oncological tracer used to perform Positron Emission Tomography y ([18F]FDHT PET) scans. A series of radiotracers has been developed to visualize the androgen receptor of which 16-beta-[18F]-fluoro-5-alphadihydrotestosterone was selected for clinical evaluation. Dihydrotestosterone is the predominant form of testosterone in the prostate gland. Biodistribution studies in rats and baboons showed prostate-to-blood activity concentration ratios up to 7:1, and androgen receptor binding. The activity of FDHT in the region of the prostate peaked at 30-90 minutes post injection. At 60 minutes there was a high ratio of prostatic activity to soft tissue, blood and bone (>6:1, >3.5:1 and >7:1 respectively). Uptake decreases after the administration of cold testosterone. However, time

course studies have not been conducted in relation to treatment and response. A noninvasive method for measuring changes in the androgen receptor (AR) in metastatic prostate cancer may be particularly important for assessing the effects of drugs that act through or directly on the androgen receptor.

Accurate quantification of the [18F]FDHT signal is important beyond visual image interpretation. For quantification of PET tracers, non-linear regression analysis is the gold standard. However, its complexity makes it unsuitable for application in daily clinical practice; moreover, it is not compatible with the whole body acquisitions typically required in patients with metastasized disease. Simplified measures applicable in whole body settings can and should be validated versus the reference technique. Perfusion related parameters are often important in pharmacokinetic modeling. Sofar, we have used 15O-water PET to measure these variables. However, [15O]-water PET requires an on-site cyclotron, and this is not available in the majority of hospitals.
Alternatively, DCE-MRI is a clinically available, and it measures perfusion-related parameters as well. However, it needs to be shown how these DCE-MRI parameters correlate with [15O]-water PET. We expect that, upon validation, incorporation of DCE-MRI will provide an even more comprehensive multiparametric quantitative image since this adds information on permeability and perfusion and with higher spatial resolution than is feasible with PET.

Taken together, a profound understanding of the [18F]FDHT pharmacokinetics could lead to an optimization of the [18F]FDHT PET diagnostic potential; integration of DCE MRI and PET parameters would allow for a clinically feasible method with PET-MRI. This is essential to improve the quality of the imaging research towards personalized therapy strategies for prostate cancer patients.

Study objective

The objectives of this trial are:
1. To define the performance characteristics of FDHT PET in patients with metastasized castrate resistant prostate cancer
(mCRPC).
(a) To demonstrate the kinetics of displacement of the tracer off of the androgen receptor(AR) in patients treated with enzalutamide.
(b) To demonstrate the variability of the imaging characteristics
(c) To preliminary explore early post-treatment changes in FDHT and PSMA uptake and MRI in patients treated with abiraterone and other androgen biosynthesis inhibitors.
(d) To explore predictive value of baseline FDHT and PSMA uptake before AR-targeted treatment.
2. To define the relationship between FDHT uptake and PSMA uptake and tumor diffusivity as assessed by whole-body MRI.
3. To define the relationship between FDHT uptake, AR expression, serum androgen levels, androgen levels in biopsy specimens, CTC enumeration, ARV7 presence, and ARV7 nuclear localization.

Sub-study:
The aims of the sub-study are to create a tracer kinetic model for quantification of [18F]FDHT, to simultaneously validate a simplified quantitative method, and to investigate the concordance of MRI- and PET-based perfusion related parameters.

Study design

This is a multi-center, prospective observational study in 105 patients with metastasized castrate resistant prostate cancer. Reproducibility and variablitiy of FDHT-PET will be addressed using a test-retest FDHT-PET study without intercurrent treatment on day 1 and 2. If unstable FDHT scans (a relative difference is recorded of more than 0.15 in 5 patients or more) patients will be scanned at day 1 and 8. When still unstable patients will be scanned at day 1 and 22. However if there is a relative difference is less than 0.15 the cohort will be expanded with an additional 50 patients. All patients wil also undergo a DW-MRI at baseline to define the correlation between FDHT and tumor diffusity.

Patients in the expanded cohort will undergo one baseline FDHT-PET, DW-MRI, and/or PSMA PET before start of AR-targeted therapy, one PSMA-PET and/or DW-MRI 4 weeks after start of treatment and one DW-MRI and or PSMA PET at progression. These will serve to explore the predictive value of FDHT PET and postreatment changes in PSMA-PET and DW-MRI. Blood is taken to define the relationship between FDHT uptake, serum androgen levels, CTC enumeration, ARV7 presence, and ARV7 nuclear localization. Optional FDHT guided biopsy is performed to correlate FDHT-PET and serum androgen levels with AR expression and androgen levels in biopsy specimens.

Sub-study:
A monocenter, prospective observational study in 10 patients with metastasized castrate resistant prostate cancer. Dihydrotestosterone uptake [18F]FDHT, perfusion ([15O]-water), and DCE-MRI parameters will be measured quantitatively. Accuracy of blood and plasma activity concentration, plasma metabolite measurements derived from arterial and venous samples as well as the reliability of using Image Derived Input Functions (IDIF) for quantification of [18F]FDHT kinetics will be tested. Dynamic PET and MRI scanning will be performed using 2 tracers for PET ([15O]-water and [18F]FDHT) and 1 contrast agent for MRI (Gadovist).

Study burden and risks

The total radiation dose will be between 20 and 31 mSv. Although this is relatively high we think that it is acceptable for this particular study in view of this specific population and high scientific impact. Cannulation of the

venous canulla will be performed by experienced clinicians who have followed training at the Department of Anesthesiology. In spite of this, occasionally these cannulae may cause a hematoma. The biopsy of a metastasis will be performed under local anesthesia by an experienced interventional radiologist (CT-guided).

Sub-study:
The total radiation burden of the extra scan will be about 0.5 mSv making the total radiation dose between 14.5 mSv and 23.5 mSv. The extra scan will only be performed in patients not undergoing an PSMA scan. Cannulation of the venous en arterial cannulae will be performed by experienced clinicians who have followed training at the Department of Anesthesiology. In spite of this, occasionally these cannulae may cause a hematoma.

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

1: Histologically or cytologically proven metastatic CRPC.
2. Progressive disease based on any of the following:
(a) a rise in PSA through 3 consecutive measurements
(b) progressive disease by virtue of transaxial imaging based on RECIST 1.1
(c) radionuclide bone scan showing at least two new metastatic lesions.
3. Patients will have castrate levels of serum testosterone <= 50 ng/dL.
4. Written informed consent, Substudy:
1. Inclusion in the Movember GAP2 project
2. Written informed consent
3. Patients have to be able to remain supine for 70 minutes

Exclusion criteria

1. Patients already on enzalutamide or other antiandrogens
2. Contraindications for MRI, Sub-study
1. Claustrophobia
2. Multiple malignancies
3. Hb < 6.0 mmol/L
4. Renal insufficiency (GFR < 30 mL/min/1.73m2)
5. Known hypersensitivity to Gadovist

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-02-2015
Enrollment:	36

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	[15O]-Water
Generic name:	[15O]-H2O
Product type:	Medicine
Brand name:	FDHT
Generic name:	[18-F]-Fluorodihydrotestosterone
Product type:	Medicine
Brand name:	PSMA
Generic name:	[18F] DCFPyL

Ethics review

Approved WMO Date:	06-08-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	27-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	14-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2021
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	EUCTR2014-001600-21-NL
CCMO	NL48923.029.14