Pilot Study assessing sildenafil effect on lung tumour blood flow

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The aim of this pilot study is to assess if the sildenafil leads to an increase in tumour blood flow in NSCLC.

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON31434

Source
ToetsingOnline

Brief title
sildenafil tumour perfusion

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

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: de kosten worden door de longafdeling gedragen

Intervention

Keyword: lung cancer, perfusion, sildenafiil citrate

Outcome measures

Primary outcome

The baseline and post-sildenafil tumour perfusion will be compared using the

Wilcoxon signed-rank test to assess any change in tumour perfusion.

Secondary outcome

not applicable

Study description

Background summary

Patients with non-small cell lung cancer (NSCLC) have a 5 -year survival rate of 15%. The worst prognosis is seen in stages IIIb and IV: 1-year survival of 23-46%. Combined chemotherapy with a platinumderivative and a 3rd generation cytotoxic agent is currently the standard treatment of stages IIIb and IV. This improves quality of life but only improves 1-year survival by 10%. There is thus a great need to improve treatment outcome in patients with advanced or metastatic NSCLC. One possible approach may be to (transiently) increase tumour perfusion, as this should enhance chemotherapy delivery and thus efficacy. In addition, hypoxic conditions due to vascular insufficiency exist in solid cancers and appear to be associated with resistance to both radiotherapy and chemotherapy. The associated improved tumour oxygenation may therefore also lead to chemosensitisation and radiosensitisation.

Sildenafil is a highly selective phosphodiesterase type 5 (PDE5) inhibitor. PDE5 is a member of the superfamily of phosphodiesterases that specifically cleaves and thereby inactivates cyclic guanosine monophosphate (cGMP). cGMP is the intracellular 2nd messanger of nitric oxide (NO) and the main mediator of smooth muscle relaxation and vasodilatation. By inhibiting the cleavage of cGMP sildenafil prolongs its action and thus augments smooth-muscle relaxation and vasodilatation. Recently it has been shown to act on the pulmonary vasculature, causing pulmonary vasodilatation, and has been approved for the treatment of pulmonary arterial hypertension.

No previous studies have assessed whether sildenafil induced pulmonary

vasodilation leads to an associated increase in lung tumour perfusion. If this were to be the case then sildenafil could potentially be a chemo-en/or radiosensitiser as explained above.

Study objective

The aim of this pilot study is to assess if the sildenafil leads to an increase in tumour blood flow in NSCLC.

Study design

After inclusion baseline blood pressure, pulse and hematological, renal and hepatic functions will be determined. Women of childbearing potential will additionally undergo a pregnancy test. A baseline dynamic CT perfusion scan and water-PET scan will be performed to assess baseline tumour perfusion. On the treatment day patients will receive 50 mg sildenafil orally (time point 0). One hour after administration a CT perfusion and water-PET scan will be performed to assess tumour perfusion post sildenafil. By comparing the baseline and post-treatment scans the effect on tumour perfusion will be estimated. Blood pressure and pulse will be monitored at 0, 15, 30, 45, 60 and 120 mins to assess for possible systemic hypotension.

Intervention

Administration of 50mg sildenafil.

Study burden and risks

The extra burden for the patients consists of one extra hospital visit lasting approximately 2 hours during which the patient receives a 50 mg tablet of sildenafil and a dynamic CT perfusion and PET scan. De baseline perfusion scan and bloods will be conducted during a previously planned visit as part of their tmour staging/treatment. The extra radiation dose of the perfusion scan is estimated at 1,3 mSv and the PET scan at 1.8mSv.

Sildenafil has a good safety profile. Common side effects are headache, nausea, dyspepsia, rhinitis, flushing, dizziness and asymptomatic decrease in blood pressure. Episodes of dose related abnormal vision (blurred vision, changes in light perception and transient blue-green vision) have been reported but they were usually reversible. Rare cases of non-arteretic ischaemic optic neuropathy (NAION) have been reported in patients using sildenafil but a causative relationship has not been established. To minimise this risk patients with a history of visual loss and genetic degenerative retinal disease e.g. retinitis pigmentosa will be excluded.

Contacts

Public
Vrije Universiteit Medisch Centrum

boelelaan 1117
1007 MB aAmsterdam
NL
Scientific
Vrije Universiteit Medisch Centrum

boelelaan 1117
1007 MB aAmsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age > 18 years
2. WHO performance status 0-1
3. Adequate hematological, renal and hepatic functions
a. total bilirubin < 1.5 x UNL
b. ASAT/ALAT < 2 x UNL
c. alkaline phosphatase < 5 x UNL
d. creatinine < 130 mmol/L
4. Primary tumour size >=3cm
5. Written informed consent

Exclusion criteria

1. Concurrent NTG, ritonivir, azoles, other P450 inhibitors
2. Concurrent anti-hypertensive or nitrate medications
3. Hypersensitivity to sildenafil/component of formulation
4. Contrast allergy
5. Hypotension <90/50mmg
6. Other serious diseases such as heart failure, unstable angina, MI/CVA/serious arrhythmia within 6 months, diabetes
7. History of visual loss and genetic degenerative retinal disease e.g. retinitis pigmentosa
8. Pregnancy/lactation

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2007
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	viagra
Generic name:	sildenafil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-11-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2008
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	EUCTR2007-004607-35-NL
CCMO	NL19318.029.07