Nitroglycerin as a sensitizer in the treatment of non small cell lung cancer: ;a phase II trial.

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Demonstrate an increase of 2-year overall survival (OS) of 15 % (from 50% to 65 %) vs historical controls of the addition of nitroglycerin to radiotherapy (±chemotherapy) of stage I-IV NSCLC.

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

Summary

ID

NL-OMON39504

Source
ToetsingOnline

Brief title
Nitroglycerine phase II

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
non-small cell lung cancer, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: EU project Metoxia

Intervention

Keyword: Hypoxia, Nitroglycerin, NSCLC, Perfusion

Outcome measures

Primary outcome

- Demonstrate an absolute increase in 2 year overall survival of 15 % vs

historical controls

Secondary outcome

- Decrease of hypoxia (less uptake of HX-4 in the tumor) on PET-scan described

by TBR

- Tumor perfusion (of the largest lesion tumor/ node) on DCECT-scan described

by Whole tumour Blood Volume and Tumour Permeability

- Evaluating prognostic effect of perfusion and hypoxia values in patients

treated with nitroglycerin.

- Acute toxicity (CTC AE 4.0)

- Evaluate response on an 18-FDG PET-CT scan 2.5 months after the end of

treatment and correlate these findings with pre-radiotherapy FDG / hypoxia

PET-scans and perfusion CT scans.

Study description

Background summary

Tumor hypoxia is a well known factor negatively influencing the response of numerous types of cancer to chemotherapy or radiotherapy. Tumor hypoxia is due to many factors, which can be patient-related (eg. anaemia or vascular insufficiency), but also tumor-related (eg. abnormal tumor vasculature).

The primary physiological function of the tumor vasculature is to support

perfusion, the nutritive flow of blood through the tissues. Vascular physiology can be studied non-invasively in human subjects using imaging methods such as positron emission tomography (PET), magnetic resonance imaging (MRI), X-ray computed tomography (CT), and Doppler ultrasound (DU). [1-4] Tumor perfusion has a prognostic value but is also a key process to allow drug penetration in tumor tissues.

Nitroglycerin is a nitric oxide donor which is mainly known as a vasodilating agent used in ischemic heart disease. It has also been shown to increase tumor blood flow in animal and human tumors.

The addition of nitroglycerin to chemotherapy in non small cell lung cancer has been shown to generate very favorable response rates with respect to standard treatment schedules[5]. Theoretically nitroglycerin might reduce resistance to chemotherapy via a plethora of different effects: better tumor perfusion, direct effects of NO on cancer cells, increase in activated p53 protein and via an increased blood flow in the tumor with as consequence a higher drug concentration in the tumor [6].

In mice, NO donors such as isosorbide dinitrate have been shown to decrease tumor hypoxia by better tumor perfusion, which could enhance radiotherapy responses [7].

The promising results of the combination of nitroglycerin with chemotherapy and the theoretical and preclinical basis for a hypoxia reducing and radiosensitizing effect on cancer cells, make this an interesting compound to investigate in a phase II trial.

Primary endpoint of this trial will be to demonstrate a survival benefit of the addition of nitroglycerin to radiotherapy for NSCLC.

Translational research will be a part of this trial: by performing in 10 patients upfront measurements of perfusion and hypoxia and quantifying the effect of nitroglycerin on these measurements we hope to clarify the mechanism of action of nitroglycerin in NSCLC.

During this trial, acute toxicity will be monitored closely during and after radiotherapy

Study objective

Demonstrate an increase of 2-year overall survival (OS) of 15 % (from 50% to 65 %) vs historical controls of the addition of nitroglycerin to radiotherapy (±chemotherapy) of stage I-IV NSCLC.

Study design

Single centre non-randomized phase 2 trial.

Intervention

* Day 1:
- Dynamic Contrast Enhanced (DCE) CT scan at radiology department before HX-4 scan
- Injection of HX-4 at nuclear medicine department
- Static HX-4 PET-CT scan 240 minutes post-injection

The baseline DCE-CT scans and the scans after nitroglycerin are to be kept a minimum of 2 days apart to avoid renal impairment by consecutive IV contrast infusions.

Practical:

Day 3/4:
- Nitroglycerin patch Transiderm Nitro 5 at 8.30 h.
- Dynamic Contrast Enhanced (DCE) CT scan at radiology department at 14:30 h.
- Injection of HX-4 at nuclear medicine department at 15 h.
- Static HX-4 PET-CT scan 240 minutes post-injection at 19 h.
- Removal of nitroglycerin patch after scanning is completed.

Patients will receive a standard low dose nitroglycerin patch, for 12 hours daily during the whole course of radiotherapy.
2,5 months after treatment, an 18-FDG PET CT scan will be performed. These findings will be correlated with the FDG/hypoxia PET-scans and perfusion CT scans.

Study burden and risks

The extra burden in this trial consists of

- nitroglycerin patch from day 1 of radiotherapy to the last day of radiotherapy

2 DCE CT scans (1 with and 1 without nitroglycerin) AND 2 HX-4 PET-scans ((1 with and 1 without nitroglycerin) in 40 patients.
1 DCE CT scan and 1 HX-4 PET scan without nitroglycerin in 20 patients.

Risks: DCE-CT scans and HX-4 PET-CT-scans will add on average 7-7.5 and 20-25 mSV respectively to the radiation dose received [8]
When compared to the 65000 mGy which is on average administered to patients treated with radiotherapy for NSCLC at Maastro Clinic, this added radiation dose by the extra scans is negligible.

Contrast enhancement has the known risks of allergy and renal failure, which is generally a low risk. To minimize the risk of renal impairment by a bolus injection of contrast used in DCE-CT scanning, the DCE-CT scans are performed with a minimum of 48 hours apart and patients are encouraged to augment their fluid intake between scans.

Nitroglycerin has as most common side effects: headache (60% of patients), light-headedness (6% of patients), syncope (4% of patients).

The combination of nitroglycerin with chemotherapy has been proven to be safe in a large phase II trial and reports of toxicity of the combination of nitroglycerin and radiotherapy have never been made. However, theoretically the perfusion of normal tissue might also be influenced, leading to enhanced radiosensitivity of normal tissue.

Therefore patients will be closely monitored for enhanced side effects during and after radiotherapy. A stopping rule has been foreseen in case of excess toxicity.

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

- Non-small cell lung cancer stage IB-IV amenable for radiotherapy with curative intent.
- (Stage IV patients with oligometastatic (1-4 metastases) NSCLC are regularly treated radically in the IKL region)
- Patients not included in the PET-boost trial.
- WHO performance status 0-2
- Willing and able to comply with the study prescriptions
- 18 years or older
- Ability to give and having given written informed consent before patient registration
- No recent (less than 3 months) severe cardiac disease (NYHA class higher than 1) (congestive heart failure, infarction)
- No radiotherapy in 4 weeks prior to this study
- No treatment with investigational drugs in 4 weeks prior to or during this study.
- No known allergy to nitroglycerin or nitroglycerin patch.
- No known allergy to iodine based contrast agents
- No use of vaso-dilators (calcium channel blockers, nitrates or 5-fosfodiesterase inhibitors)
- No symptomatic hypotension
- No other active malignancy
- No major surgery (excluding diagnostic procedures like e.g. mediastinoscopy) in previous 4 weeks
- Adequate renal function: calculated creatinine clearance at least 60 ml/min

Exclusion criteria

The opposite of the above

Study design

Design

Study phase:	2
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-12-2011
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	HX4
Generic name:	HX4
Product type:	Medicine
Brand name:	Nitroglycerin Patch
Generic name:	nitroglycerin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	11-10-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	18-10-2011
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO

Date:	22-08-2012
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-09-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-03-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2010-023120-24-NL
ClinicalTrials.gov	NCT01210378
CCMO	NL34135.068.10