Hydroxychloroquine as an anti-autophagy and chromatin modulating drug in combination with erlotinib in non-small cell lung cancer (NSCLC) patients: a single-center single arm open-label phase II trial

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To evaluate the efficacy of the drug combination. Translational work is aimed to explore pharmacodynamic, predictive and surrogate endpoint biomarkers in tumor tissue and blood.

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

Summary

ID

NL-OMON37508

Source
ToetsingOnline

Brief title
Hydroxychloroquine and erlotinib in NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Advanced stage NSCLC, Metastatic NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Autophagy, Erlotinib, Hydroxychloroquine, NSCLC

Outcome measures

Primary outcome

The difference in metabolic activity of the tumor after one week of treatment as compared to the baseline value, measured with 18F-FDG PET using predefined PET response criteria.

Secondary outcome

* To assess the disease control rate (DCR) according to the response evaluation criteria in solid tumors (RECIST v1.1) with CT-Thorax, performance free survival (PFS) after six months of treatment and overall survival (OS) after one year of treatment.

* To assess the level of autophagy at baseline and the inhibition of autophagy during treatment in peripheral blood and tumor samples.

* Upon progression, a rebiopsy will be taken to analyse EGFR mutation and autophagy status and to analyse mechanisms of secondary resistance to erlotinib/hydroxychloroquine treatment.

Study description

Background summary

Less than 30% of patients with metastatic NSCLC respond to standard

platinum-based doublet chemotherapy. In addition, the side-effect profile of this treatment is far from satisfactory.
EGFR TKI (epidermal growth factor receptor tyrosine kinase inhibitor) treatment is associated with a favorable side-effect profile. However, patients either possess primary resistance to EGFR-TKIs or develop secondary resistance during the course of anti-EGFR treatment. Preclinical work has shown that the combination of hydroxychloroquine (HCQ) and erlotinib has the ability to overcome primary and secondary resistance to EGFR TKIs. Chromatin modulation en autophagy inhibition by HCQ seem to be the responsible mechanisms that cause (re)sensitization of tumor cells for erlotinib.

Study objective

To evaluate the efficacy of the drug combination. Translational work is aimed to explore pharmacodynamic, predictive and surrogate endpoint biomarkers in tumor tissue and blood.

Study design

Single-center single arm open-label phase II study.

Intervention

Erlotinib 150 mg once daily and HCQ 1000 mg once daily.

Study burden and risks

Wide experience exists with the prescription of both drugs and both drugs have been found to be save when prescribed. A recent Phase I study showed that the combination ican be given safely with an acceptable toxicity profile. Patients accrued to the study will have to visit the outpatient department 3-weekly, where a case record form (CRF) will be filled out and blood will be drawn. A PET-CT scan and tumor biopsy will be performed at baseline and after one week of treatment. The amount and schedule of investigations are not different from routine clinical practice, except for the two PET-CT scans and the tumor biopsy after one week of treatment.

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

* Histologically confirmed stage IV non-squamous NSCLC patients.
* Patients:
with an activating EGFR mutation who progressed on erlotinib or gefitinib monotherapy.
OR
who failed after at least one line of platinum based doublet chemotherapy and who are EGFR TKI naïve.
* At least one measurable disease site, defined as a lesion of * 1 cm in at least one dimension on CT-scan.
* WHO performance status 0-2.
* No symptomatic brain metastases.
* Absolute neutrophil count of at least 1500/*l, platelet count of at least 100000/*l and hemoglobin level at least 6 mmol/l.
* Calculated creatinine clearance of at least 60 ml/min.
* Adequate hepatic function: Total bilirubin * 1.5 x upper limit of normal (ULN); ALT, AST, and alkaline phosphatase * 2.5 x ULN (in case of liver metastases * 5 x ULN).
* Willing and able to comply with the study prescriptions
* 18 years or older.
* Not pregnant or breast feeding and willing to take adequate contraceptive measures during the study.
* Ability to give and having given written informed consent before patient registration.

* No recent (< 3 months) severe (NYHA class >1) cardiac disease (congestive heart failure, infarction). No history of cardiac arrythmia (multifocal premature ventricular contractions, uncontrolled atrial fibrillation, bigeminy, trigeminy, ventricular tachycardia) which is symptomatic and requiring treatment (CTC AE 4.0), or asymptomatic sustained ventricular tachycardia. Asymptomatic atrial fibrillation controlled on medication is allowed.
* No cardiac conduction disturbances or medication potentially causing them: congenital long QT-syndrome or unexplained sudden death of first degree relative under 40 years of age, QT interval > 480 msec (note: when this is the case on screening ECG, the ECG may be repeated twice. If the average QT-interval of these 3 measurements remains below 480 msec, patient is eligible). Patients on medication potentially prolonging the QT-interval are excluded if the QT-interval is > 460 msec. Medication that might cause QT-prolongation or Torsades de pointes tachycardia is not allowed. Drugs with a risk of prolonging the QT-interval that cannot be discontinued are allowed, however, under close monitoring by the treating physician.
* No uncontrolled infectious disease.
* No clinically significant gastrointestinal abnormalities.
* No other active malignancy.
* No major surgery (excluding diagnostic procedures like e.g. mediastinoscopy or VATS biopsy) in the previous 4 weeks.
* No treatment with investigational drugs in the 4 weeks prior to or during this study that are thought or known to interact with autophagy or the EGFR axis.
* No known G6PD deficiency.
* No psoriasis or porphyria.
* No known hypersensitivity to 4-aminoquinoline compound.
* No retinal or visual field changes from prior 4-aminoquinoline compound use.
* No known prior hypersensitivity to erlotinib, HCQ or any of their components.

Exclusion criteria

We refer to the inclusion criteria

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-07-2012
Enrollment:	136
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Plaquenil
Generic name:	Hydroxychloroquine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tarceva
Generic name:	Erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-02-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-05-2012
Application type:	First submission
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

ID: 21406
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2011-004903-20-NL
CCMO	NL38376.029.12
OMON	NL-OMON21406