Open-label, randomised, multi-center study investigating Cetuximab, in combination with concurrent chemo- / radiotherapy in locally advanced non-small cell lung carcinoma

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

Summary

ID

NL-OMON32353

Source
ToetsingOnline

Brief title
Cetuximab with concurrent chemo-/radiotherapy in stage II/III NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Merck

Intervention

Keyword: cetuximab, cisplatin, non-small cell lung carcinoma, radiotherapy

Outcome measures

Primary outcome

Phase I: Adverse events (dose-limiting toxicities are defined in Paragraph 9.4)

Phase 2: Objective tumour response (According to RECIST)

Secondary outcome

Overall survival (OS)

Progression free survival (PFS)

Duration of overall response

Safety

Assessment of predictors of response:

o EGFR-IHC, EGFR-mutation analysis, KRAS-mutation analysis

o ERCC-1 immunohistochemistry

o FDG-PET

o Molecular/biological parameters (serum tumour markers)

Study description

Background summary

Lung cancer is the leading cause of cancer related death. Despite worldwide efforts the survival has not improved much in contrast to many other types of malignancies. In non-small cell lung carcinoma (NSCLC), as in most other

malignancies, therapy depends on the extent of the disease. Early stage disease, without nodal metastases can be operated depending on the size and local invasion of the tumour. Surgery alone is inadequate if lymph node metastases are present. Thirty percent of patients present with locally advanced NSCLC (stage IIIa and IIIb without pleural effusion). Since the early eighties various combinations of chemotherapy (CT) and surgery, and CT and radiotherapy (RT) with/without surgery have been tested. Both sequential (CT followed by RT) and concurrent chemoradiotherapy (CRT) showed to be superior to RT alone. Several comparative studies have shown that concurrent CRT is superior over the sequential approach, however at the cost of higher albeit acceptable toxicity. A recent meta analysis on CRT showed an absolute 3-years overall survival benefit of 6.6% for concurrent over sequential CRT due to improved local control.
The Epidermal Growth Factor Receptor (EGFR) is a transmembrane glycoprotein, which is commonly expressed, in many normal human tissues. This receptor is over-expressed on many solid tumours including NSCLC. Abnormal signalling via this receptor has been associated with an unfavourably outcome of disease. Vice versa, inhibition of this receptor can favourably influence tumour growth and induce objective responses in a subset of patients, depending on clinical and molecular parameters .
Cetuximab is a targeted therapeutic agent, a chimeric IgG1 monoclonal antibody that specifically binds to the EGFR with high affinity, internalising the receptor and preventing the ligands EGF and TGF-α from interacting with the receptors and thus effectively blocking ligand-induced EGFR phosphorylation. In addition, Cetuximab has been found to potentiate the effects of chemotherapy and radiotherapy in experimental systems. Cetuximab (ERBITUX®) has been approved and is available in the United States, European Union, Switzerland and over 50 countries worldwide.

Study objective

The aim of the study is to assess the feasibility of combined treatment of Cisplatin, Cetuximab and concurrent RT and to get insight in the clinical efficacy (for study schedule, see flow chart 1). The first phase of the study will mainly focus on the acute toxicity. The second phase of the study, which has a 2-arm randomised multi-centre phase 2 design, intends to assess both safety and clinical activity of the treatment schedules.

Study design

Patients presenting at medical oncology or radiotherapy department will be asked to participate. During the first phase of the study 12 patients will be treated simultaneously with daily-dose Cisplatin and RT in combination with weekly Cetuximab. This is followed by a waiting period of 3 months, between phase 1 and before phase 2 can start, to evaluate acute toxicity. Despite the fact that there are no major safety concerns, clear stopping rules and rules on

dose modification have been made. In the absence of major toxicity the second phase of the study will start. In the second phase patients will be randomised in a two-arm fashion for either, daily-dose Cisplatin, and RT, or daily-dose Cisplatin, RT, with Cetuximab.

Patients will be asked separately to participate in a study on early response predictors. The results of these tests will be collected prospectively and will not influence clinical decision making.

Intervention

After informed consent has been obtained the treatment plan will be finalized. During the phase 1 part of the study, *the feasibility phase*, patients will receive concurrent CRT in combination with Cetuximab. The second part of the study (Phase 2) will follow if toxicity is acceptable. During this part of the study patients will be randomised for CRT with or without Cetuximab.
The administration of study drugs should be started within 14 days after randomisation.

Study burden and risks

Skin reactions may develop in more than 80% of patients and mainly present as acne-like rash and/or, less frequently, as pruritus, dry skin, desquamation, hypertrichosis, or nail disorders (e.g. paronychia). They generally resolve, without sequelae. Approximately 15% of the skin reactions are severe, including single cases of skin necrosis. In the event of Grade 3 or 4 skin reactions the patients should be referred for dermatological advice.

The incidence of radiation dermatitis of any grade was comparable between the treatment groups in a phase 3 trail in patients with squamous cell carcinoma of the head and neck receiving RT alone (90%) or Cetuximab in combination with RT (86%).

Other side effects observed (>=10%) in patients receiving Cetuximab monotherapy include asthenia, dyspnoea, mucositis, nausea, pain, fever and headache.

Severe infusion-related reactions may occur (>= 1/100, < 1/10), in rare cases with fatal outcome. They usually develop during or within 1 hour of the initial Cetuximab infusion and may include symptoms such as rapid onset of airway obstruction (bronchospasm, stridor, hoarseness, difficulty in speaking), urticaria, hypotension, or loss of consciousness. In rare cases, angina pectoris, myocardial infarction or cardiac arrest have been observed.

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 confirmed diagnosis of NSCLC
2. Stage II/III non-operable disease , without malignant pleural effusion
3. Presence of at least one measurable target lesion
4. Life expectancy of at least 6 months
5. WHO performance 0-1
6. Signed written informed consent

Exclusion criteria

1. Concurrent active malignancy other than localized, non-melanoma skin cancer or carcinoma-in-situ of the cervix (unless definitive treatment was completed 5 years or more

before study entry and the patient has remained disease free);
2. Prior:
a. Ipsilateral radiotherapy to the chest;
b. Chemotherapy within the last 5 years;
c. Immunotherapy or treatment with murine monoclonal antibodies, Cetuximab, or other EGFR inhibitors.
3. WHO performance score > 1

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	112
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	cisplatin
Generic name:	cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-11-2007
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-02-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2007-003894-18-NL
CCMO	NL20266.031.07