Randomized phase II feasibility study of Cetuximab combined with 4 cycles of TPF followed by platinum based chemo-radiation strategies

Published: 07-03-2008
Last updated: 07-05-2024

The primary objective is to select one of two platinum strategies to be used in this regimen for use as experimental arm in Phase III. This is a screening feasibility study addressing purely investigational approaches.

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

Summary

ID

NL-OMON32191

Source
ToetsingOnline

Brief title
E24061

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
head and neck carcinoma, laryngeal cancer

Research involving
Human

Sponsors and support

Primary sponsor: EORTC
Source(s) of monetary or material Support: EORTC,Merck,Sanofi-aventis

Intervention

Keyword: cetuximab, head and neck carcinoma, induction chemotherapy, radio-chemotherapy

Outcome measures

Primary outcome

Primary endpoint will be to determine the feasibility of regimens assessed on

at least 80% of the per protocol dose intensity of the radiotherapy, the

platinum and cetuximab during the chemo-radiation part of treatment. If

delays and/or dose reductions lead to less than 80% dose intensity for at least

one of these three treatments, the patient will be counted as a failure for

this criterion.

Secondary outcome

Secondary endpoints will be toxicity, dose modifications, response rate.

Safety Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

Study description

Background summary

Head and neck carcinoma's account for about 6% of all cancers with an estimated incidence around 643,000, with 351,000 deaths worldwide in 2002. Early stages (stage I and II) achieve a 5-year disease-free survival of 80-90% with chirugie or radiotherapy. Advanced disease (stage III and IV) can be divided into local resectabele extended disease, irresectable locally extensive disease and recurrent or metastatic disease. The resectabele disease patients have been treated with surgery followed by radiotherapy. However, only 30-40% of patients can be curated. Definitive radiotherapy has been used as a primary treatment

for large irresectable local disease but the results were poor with a 5-year survival of about 10%. The reasons for the failure of therapy are local return of the disease, the occurrence of distant metastases, in addition to the occurrence of second primary tumors. These poor results of locoregional control in the treatment of locally extensive disease has led to chemotherapy in the treatment of this group of patients to improve.

These developments run along parallel roads. On the one hand, there is renewed interest in induction chemotherapy with improved chemotherapy regimens prior to the locoregional treatment. Taxanes in combination with platinum and 5FU are more effective than platinum and 5 FU in the induction chemotherapy, measured by response rate, time to treatment failure. Whether this results in a better survival to the whole group is the subject of ongoing Phase III studies, for irrecetable tumors there is a survival advantage.
Chemoradiatie with cisplatin is currently regarded as the standard treatment. Meta analysis of phase III study show that concomitant chemoradiatie gives a 8-11% survival benefit compared to radiation alone in patients with a non-resectable local comprehensive disease, in particular by improving the locoregional control.

Cetuximab has added to both radiotherapy and platinum-containing chemotherapy efficacy in this patient group show in the local advanced and in the metastatic or recurrent setting.

Study objective

The primary objective is to select one of two platinum strategies to be used in this regimen for use as experimental arm in Phase III. This is a screening feasibility study addressing purely investigational approaches.

Study design

The schema here under illustrates the trial design:
2 cycles of TPF will be administered. In absence of progression, patients will be treated with 2 additional cycles of TPF. In case of SD/PR/CR after 4 cycles, then chemoradiation will be given. If less than SD, patients will go off study. The maximal two weeks of delay will be allowed between last cycle of TPF and start of radiotherapy (maximal 5 weeks from the start of
last cycle of TPF treatment). All patients will receive concomitant cetuximab at doses as explained below.
Arm 1: Induction chemotherapy with TPF followed by concomitant chemoradiotherapy with weekly cisplatin.
Arm 2: Induction chemotherapy with TPF followed by concomitant chemoradiotherapy with weekly carboplatin.
Both arms are given with cetuximab throughout, given with a loading dose of 400mg/m2 and then 250mg/m2 weekly.

Intervention

induction chemotherapy with TPF followed by chemoradiation with weekly cisplatin or carboplatin in combination with Cetuximab. Randomisation to cisplatin or carboplatin.

Study burden and risks

The agents which will be given to you may have various types of side effects.
For Docetaxel, the most frequent side effect is a temporary decrease in white blood cells
(granulocytes) which help to fight infection.
Almost all patients will experience reversible hair loss and fatigue. Skin reactions,
low blood pressure or other allergic reactions might occur while the drug is being given. These symptoms are reversible and will be treated if they occur.
Cisplatin and carboplatin may mostly generate myelosuppression, hearing loss and renal functions
problems as well as neurological problems such as paresthesia, although appearing to a lesser extend with Carboplatin
5-FU may induce oral mucositis, diarrhea, hand-foot syndrome, cardiac ischemia and photosensibilisation.
Radiotherapy may cause redness or soreness of the skin of the irradiated area and fatigue. It may lead to dental deterioration.
Even though Cetuximab has been given to more than 2300 patients in clinical trials, we still need
additional studies to understand how best to use this drug. We do not know all of the side effects of
the study drug when used alone or when it is combined with other drugs.
In other studies conducted in cancer patients and healthy volunteers treated with Cetuximab, the
most common side effects were: rash (some look like acne), fatigue, nausea, diarrhea, headache,
fever, dyspnea, flu symptoms and vomiting, hypomagnesemia.Other side effects reported in these trials include: shortness of breath, difficulty in sleeping, flatulence, stomach cramps, anemia, loss of appetite, facial flushing, mouth ulcer, powdery taste, back pain and abnormal liver function tests.
The potential exists for infusion reactions to occur during or following administration of cetuximab.
In clinical trials, severe hypersensitivity reactions characterized by the rapid onset of airway
obstruction, urticaria, and/or hypotension, have been observed in 2.7% of patients treated with
cetuximab. If it is occurred, appropriate medical therapy will be available for use in the treatment of
such reactions.

Serious events that have been reported in 12.1% of patients include abdominal pain, allergic reaction, asthenia, fever. They were easily controlled with appropriate medical
therapy.
Currently amongst the Cetuximab trials (more than 2300 patients) there have been 1 death thought
to be due to drug related toxicities/events. During the study you will therefore be followed
extremely closely for side effects.
The effects of treatment on an embryo or fetus were evaluated in pregnant monkeys. In this study,
Cetuximab did not cause developmental toxicity in fetuses even at maternally toxic doses.
However, because there is no evident data in human, pregnant women cannot participate in this
study. Also, breast-feeding is not allowed during the study as this may result in exposure of the child to treatment.
Risks associated with drawing blood from your arm include pain, bruising, lightheadedness, and on
rare occasions, infection. The MRI, CT and bone scans your doctor will obtain will expose you to
small doses of radiation. For some people the dyes used for MRI, CT and bone scans can cause an
allergic reaction.

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 proven newly diagnosed unresectable squamous cell carcinoma of the head and neck.
-Patients who have uni- or bidimensionally measurable disease.
- Patients must consent to access of their skin material for EGFR status and downstream signaling.
- Stage III or IV.
- Absence of distant metastasis
- Patients who have unresectable disease
- No prior treatment for head and neck cancer
- No nasopharynx, nasal and paranasal cancer
- Age 18-75
- WHO Performance Status 0 or 1
- Normal hematological functions: neutrophils * 1.5 x109 cells/l, platelets * 100 x109 cells/l.
- Normal liver functions: bilirubin < 1.5 times the upper limit of the normal range; alkaline phosphatase and transaminases < 2.5 times the upper limit of the normal range.
- Serum creatinine < 120 *mol/l (< 1.36mg/dl) and calculated CrCl * 60ml/min
- Patients having normal cardiac function(LVEF * 50%), clinically satisfactory 12 lead ECG, and in the past 6 months no serious cardiac illness or medical condition
- All patients (male and female) must use effective contraception methods according to CPMP/ICH/286/95 if of reproductive potential (e.g. implants, injectables, combined oral contraceptives, IUDs, sexual abstinence or vasectomised partner).
- Females must not be pregnant or lactating.
- No current malignancies at other sites with the exception of cone biopsied carcinoma of the cervix and adequately treated basal or squamous cell skin carcinoma or other cancer from which the patient has been disease-free for at least last five years.
- Absence of any unstable systemic diseases or active uncontrolled infections.
- Patients may not receive any anticancer therapy, or other investigational agents while on study.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be assessed with the patient before registration in the trial.
- Before patient registration/randomization, written informed consent must be given

according to ICH/GCP, and national/local regulations.
- Patients can only be registered/randomized in this trial once.

Exclusion criteria

see above

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-01-2009
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	carboplatin
Generic name:	carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	ciprofloxacin
Generic name:	ciprofloxacin

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	cisplatin
Generic name:	cisplatinum
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	erbitux
Generic name:	Cetuximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Taxotere
Generic name:	decetaxel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-03-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-06-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-07-2010
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
Other	2006-004189-14
EudraCT	EUCTR2006-004189-14-NL
CCMO	NL22152.029.08