A blind randomized multicenter study of accelerated fractionated chemo-radiotherapy with or without the hypoxic radiosensitizer nimorazole (Nimoral), using a 15 gene signature for hypoxia in the treatment of squamous cell carcinoma of the head and neck.

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

Summary

ID

NL-OMON45227

Source
ToetsingOnline

Brief title
EORTC 1219 H&N nimorazol study

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym

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squamous cell carcinoma of the head and neck; head and neck cancer

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: European Organisation for Reasearch and Treatment of Cancer (EORTC)

Intervention

Keyword: accelerated fractionated chemo-radiotherapy, gene profile, head and neck cancer, hypoxic radiosensitizer Nimorazol

Outcome measures

Primary outcome

Primary endpoint:

* Locoregional control

Secondary outcome

Secondary endpoints:

* Local control

* Regional control

* Time to distant metastases

* Overall survival

* Disease-free survival

* Disease-specific survival

* Acute and late toxicity

Study description

Background summary

The drug nimorazole belongs to a class of chemicals known as 5-nitroimidazoles. Drugs from this class are used against infection. In addition, nimorazole makes tumor cells more sensitive to radiotherapy, in particular tumor cells that are poorly oxygenized (hypoxia). Hypoxia is seen often in tumors of the head and neck and therefore this study will be performed for this tumortype. We want to find out whether the addition of nimorazole to the standard treatment with radiotherapy in combination with chemotherapy with cisplatin shows activity against head and neck cancer and is safe.
Furthermore we will investigate if a specific examination done with the tumor tissue will help to predict whether the treatment will work or not. We will examine the gene profile of the tumor tissue and test it for the so-called "15 gene profile for hypoxia". The aim is to find out whether this test can predict which patiënts are likely to respond to nimorazole.
To find out if the activity observed with this treatment is not caused by chance alone, we need to obtain data from patients who receive this treatment and from patients who don't receive this treatment, just the current standard. The data from these two groups of patients will be compared to see which treatment is better. Participants will be split into 2 groups. Each group will receive different treatments. The treatment each group receives is determined by chance using a computer program. This works like flipping a coin and is called randomization. This helps to make sure that groups of patients are similar when the study starts. For further information, please refer to section 1.1 of the study protocol.

Study objective

There are two primary objectives in this study: The first of them is to evaluate in a blinded randomized trial, whether the hypoxic cell radiosensitizer nimorazole can improve the effect of primary curative accelerated fractionated concomitant chemo-radiotherapy with concomitant cisplatin given to patients with squamous cell carcinoma of the head and neck (HNSCC) larynx, hypopharynx and HPV/p16 negative oropharynx.The second one is to investigate if the patients and tumors that may have such benefit can be predicted by the use of a hypoxic gene profile, i.e. if the treatment benefit is larger and essentially restricted to the subset of patients who are hypoxic cell signature positive.
The secondary objectives will be to evaluate the feasibility and morbidity of such treatment.

Study design

This is a randomized, placebo-controlled, multicenter, phase III study.

Intervention

Standard treatment is radiotherapy combined with chemotherapy. Radiotherapy

will be given daily (monday through friday) over a period of 6 weeks giving 6 fractions per week to a total of 35. The dose to macroscopic tumor will be 70 Gy; non-involved lymph nodes of the neck will receive an "elective" dose of 54 Gy. Cisplatin will be given either weekly: 40 mg/m2 (on day 1, 8, 15, 22, 29) or 100 mg/m2 on day 1 and day 22. Which schedule will be used is optional for each participating center.

Experimental part of the treatment:
Patients will receive nimorazole or placebo (1,2 g/m2) 90 min. (+/- 30 min) prior to each radiotherapy fraction but not more than 5 times per week. On days when two fractions will be delivered, nimorazole/placebo will only be given before the first fraction.

Study burden and risks

No extra burden with regard to time, no extra invasive examinatons
During each daytime admission for cisplatin administration there wil be an extra physical examination by a neurologist.
Potential side effects of nimorazole:
* Nausea
* Vomiting
* Diarrhea
* Allergic reactions including skin rash and itching
* Overdosage can cause epileptic seizures and other neurologic symptoms.

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

* Before patient registration, written informed consent must be given according to ICH/GCP, and national/local regulations
* Newly diagnosed tumors classified as stage III-IV located in the larynx, oropharynx and hypopharynx
* HPV/p16 negative (*70% positively stained cells), assessed locally for tumors of the oropharynx.
* Tumors of the larynx and hypopharynx regardless of the HPV status.
* Histopathological diagnosis of invasive squamous cell carcinoma in the primary tumor.
* No distant metastasis (M0).
* Age * 18 years.
* Tumor material available for central testing of the hypoxic gene signature
* WHO performance 0-2.
* All hematology and biochemical investigations, should be done within 4 weeks before randomization (maximum 6 weeks before treatment starts)
* Normal bone marrow function based on routine blood samples, i.e. neutrophils * 1.0 x 109/L, platelets * 75 x 109/L, hemoglobin * 10.0 g/dL or 6.2 mmol/L
* Normal kidney function creatinine clearance * 60 mL/min, and Electrolyte balance: calcium * 11.5 mg/dl or 2.9 mmol/L, magnesium * 1.2 mg/dl or 0.5 mmol/L
* Normal liver function assessed by routine laboratory examinations, i.e. bilirubin < 1.5 x ULN, ALT< 3 x ULN, alkaline phosphatases < 3 x ULN
* No prior or current anticancer treatment to the head and neck area (e.g. radical attempted or tumor reductive surgery, neo-adjuvant chemotherapy, EGFR inhibitors or radiotherapy).
* Patients must be candidate for curative intent external beam chemo-radiotherapy, and must be expected to complete the treatment.
* All patients should have an oral and dental examination including preferably clinical and radiological examination. Whenever indicated, extraction of dental elements should be carried out at least 10 before treatment start; for 1-2 (max 2) monoradicular single tooth extractions (if not continous a max of 4) without bone resection 5 days (as a minimum) are allowed.
* Radiotherapy planned to start within acceptable delay (preferably within 2 weeks and a maximum of 4 weeks from randomization).
* Radiotherapy planned to start within 8 weeks from baseline imaging tumor assessment.

* Patients should not have symptoms of peripheral neuropathy, assessed by medical history.
* Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before randomization in the trial.
* All subjects must:
* Agree to abstain from donating blood while receiving therapy and for four weeks following discontinuation of therapy.
* Agree not to share study medication with another person and to return all unused study drug to the investigator.

Exclusion criteria

* Patients who have received treatment with any investigational drug substance within 4 weeks prior to randomization.
* Current participation in any other interventional clinical study.
* Pregnant or breast-feeding female patient. Pregnancy test should be done within 72 hours from treatment start.
* Female subjects of childbearing potential (defined as a sexually mature woman who 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally post-menopausal (amenorrhoea following cancer therapy does not rule out childbearing potential) for at least 12 consecutive months (i.e. has had menses at any time in the preceding 12 consecutive months)) not willing to use adequate contraception during study and for 6 month after last dose of study drug.
* Male subjects not willing to use condoms throughout study drug therapy, and for 6 months after cessation of study therapy if their partner is of childbearing potential and has no contraception.
* Known or suspected HIV infection.
* Second malignancies within the 3 years prior to study entry with the exception of surgically cured carcinoma in situ of the cervix, in situ breast cancer, incidental finding of stage T1a or T1b prostate cancer, and basal/squamous cell carcinoma of the skin.
* Uncontrolled or chronic bacterial, fungal or viral infection.
* Known or suspected hypersensitivity to component(s) of investigational product or cisplatin contraindication.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-12-2014
Enrollment:	170
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatin
Generic name:	cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nimoral
Generic name:	nimorazole

Ethics review

Approved WMO

Date:	12-05-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	21-07-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO

Date:	25-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	03-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2013-002441-12-NL
ClinicalTrials.gov	NCT01880359
CCMO	NL46919.091.14