Treatment optimization of cetuximab in patients with metastatic colorectal cancer based on tumour uptake of 89Zr-labeled cetuximab assessed by PET

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

Summary

ID

NL-OMON36409

Source
ToetsingOnline

Brief title
Tumour uptake of 89Zr cetuximab

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastazised colorectal cancer; advanced intestinal cancer

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: 89Zr cetuximab, advanced colorectal cancer, PET, tumour localisation

Outcome measures

Primary outcome

Part One:

The detection of 89Zr-cetuximab uptake in non-hepatic tumour lesions

(present/absent; present being defined as levels measured in ROI*s > standard

deviation of background +1).

Part two:

The % uptake (of total injected) 89Zr-cetuximab in non-hepatic tumour lesions

as measured in ROI*s corrected for background levels.

Treatment response as measured by RECIST 1.1 criteria

Secondary outcome

1) The % uptake (of total injected) 89Zr-cetuximab in liver lesions as measured

in ROI*s corrected for background levels.

2) [18F-]FDG PET measurements (SUVmax) before and after 4 weeks of treatment

with cetuximab.

3) Grade of skin toxicity as measured by predefined criteria.

Other study parameters

4) Serum magnesium levels before and during treatment.

5) EGFR saturation with cetuximab in skin samples.

6) Kinase activity in skin samples before and during treatment with cetuximab.

7) Pharmacokinetics of 89Zr-cetuximab.

Study description

Background summary

3rd line standard treatment of patients with metastatic colorectal cancer (CRC) harbouring K-ras wild type consists of anti-EGFR treatment with either cetuximab or panitumumab. This type of treatment has a modest but significant beneficial activity in this patient group with improved progression-free and overall survival. Although it is well known that patients with advanced CRC harbouring a K-Ras mutation will not respond to anti-EGFR treatment, it is not understood why patients with K-Ras wild type CRC do not all benefit from this type of therapy. In order to optimize treatment of these patients as well as health care costs, it is extremely important to identify those patients who will respond to treatment with an EGFR inhibitor at an early stage.
We hypothesize that the differences in response to treatment with cetuximab are due to variability in the pharmacokinetics and -dynamics of the antibody. Thus, we hypothesize that patients who do not respond to anti-EGFR treatment, have insufficient drug levels in tumour tissue. We hypothesize that this is due to pharmacodynamic processes such as sequestration of cetuximab in the liver which expresses high levels of EGF receptor.
With the introduction of immuno-positron emission tomography (PET), an attractive novel option to visualize molecular interactions has been developed using the combination of PET with labelled mAbs. Cetuximab labelled with zirconium-89 (89Zr) has been successfully generated (GMP) and is available for this study. Previous studies have shown excellent stability of this compound and 89Zr is shown to be safe in humans. We will use 89Zr-cetuximab to demonstrate tumour targeting by imaging and explore the relation of uptake with treatment response. With this approach we hope to achieve a better understanding of the mechanisms of action of this therapeutic mAb in metastasized CRC and eventually develop strategies that may improve efficacy of cetuximab treatment.

Study objective

The main objective of the first part of the study is the demonstration of 89Zr-cetuximab uptake in non-hepatic tumour lesions.

The main objective of the second part is the association between 89Zr-cetuximab uptake in non-hepatic tumour lesions and treatment outcome.

Secondary objectives:
1) To investigate whether there is an association between levels of uptake of 89Zr-cetuximab in the liver compared to levels of uptake in non-hepatic tumour lesions.
2) To explore whether the response observed on [18F]-FDG-PET can serve as an early response marker for future response to targeted therapy according to RECIST 1.1.
3) To explore whether there is an association between 89Zr-cetuximab uptake in non-hepatic tumour lesions, grade of skin toxicity and response according to RECIST 1.1.

Study design

Single centre, two step non-randomized intervention study

Intervention

Patients will be treated according to standard care with cetuximab. For pharmacodynamic purposes PET-imaging with 89Zr-labelled cetuximab will be performed. In addition, two [18F-]-FDG PET-CT will be performed to explore early response. Patients will undergo blood sampling and two skin biopsies for pharmacodynamic purposes of 89Zr-labelled cetuximab and kinase activity profiles, respectively.

Study burden and risks

Upon enrolment in this study, patients will be asked to undergo two skin biopsies during treatment. During therapy, follow-up will include standard laboratory analysis, immuno-PET-CT and [18F-]-FDG PET-CT on regular visits to the outpatient clinic. Side effects of the medication and adverse events as a consequence of the skin biopsies may occur. The radiation exposure is acceptable and requires no shielding after injection of 89Zr-labelled cetuximab. Patients may benefit from disease regression or stabilization as cetuximab has proven clinical benefit in this patient population.

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

Advanced colorectal adenocarcinoma
Subjects must have been treated according to standard care with a fluoropyrimidine (e.g. fluorouracil or capecitabine), irinotecan, and oxaliplatin or had contra-indications to treatment with these drugs.
Tumour material must be tested wild type for the K-Ras gene.
Subjects have at least one measurable lesion outside the liver.
ECOG Performance Status of 0, 1 or 2

Exclusion criteria

Previous exposure to an anti-EGFR therapy
Significant skin condition interfering with treatment
Insulin dependency
Concurrent anticancer chemotherapy, immunotherapy or investigational drug therapy during the study or within 4 weeks of the start of study drug.
Radiotherapy to the target lesions during study or within 4 weeks of the start of study drug. Palliative radiotherapy will be allowed.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-01-2012
Enrollment:	38
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	89Zr-cetuximab
Generic name:	cetuximab-N-succinyl-desferal-zirconium-89 (hereinafter called 89Zr-cetuximab)
Product type:	Medicine
Brand name:	Erbitux
Generic name:	cetuximab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-11-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2011
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2011
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
EudraCT	EUCTR2010-021943-41-NL
CCMO	NL33150.029.10