Pilot study to determine the effect of fractionated radiotherapy on expression of pro-angiogenic factors in oeshophagus carcinoma

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

Summary

ID

NL-OMON47705

Source
ToetsingOnline

Brief title
Angiogenic factor expression during fractionated irradiation

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
cancer in the gullet, oesophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Roche,Roche en KWF

Intervention

Keyword: Angiogenesis, Bevacizumab, Fractionated irradiation, Oesophagus carcinoma

Outcome measures

Primary outcome

The primary parameter is the alteration of the VEGF expression on mRNA level in the tumour before and during the course of neoadjuvant chemoradiation. In addition, in the bevacizumab treated cohort, the primary parameter is the activity (phosphorylation) of the VEGF receptor (VEGFR) in the tumour tissue obtained with biopsy and the microvessel density of the resection material of the tumour.

Secondary outcome

(1) Determination of mRNA expression levels of other pro-angiogenic factors than VEGF as well as pro-inflammatory factors and other factors that may influence radiosensitivity in the tumour tissue.

(2) Determination of protein expression of pro-angiogenic and pro-inflammatory factors and factors that may influence radiosensitivity in the tumour tissue with IHC.

(3) Determination of Epstein Barr virus (EBV) status in the tumour tissue.

(4) Quantification of vascular parameters in the tumour tissue to assess on-going angiogenesis.

(5) Measurement of the plasma concentration of pro-angiogenic and pro-inflammatory factors to determine if this correlates with the expression levels in the tumour tissue.

(6) Determination of the expression level of angioregulatory miRNAs in the

tumour tissue to assess whether this is affected during neoadjuvant

chemoradiation.

(7) Immune cell profiling by flow cytometric analysis (FACS)

Study description

Background summary

Evidence is emerging that the effect of radiotherapy might be enhanced by angiostatic drugs. Whereas preclinical results are promising, clinical trials have shown only moderate effect so far. This is most likely due to suboptimal scheduling; both modalities have to be precisely dosed and scheduled to gain the optimal effect, with the lowest possible toxicity. Our results show that fractionated irradiation in vitro and in vivo induces a fast and significant up-regulation of pro-angiogenic factors. These results indicate that the long term anti-tumour effects of radiotherapy might be enhanced by inhibiting the pro-angiogenic response induced during the course of radiotherapy. Whether and when this pro-angiogenic response to radiotherapy occurs in patients remains elusive. Therefore, it is important to determine the time point at which the pro-angiogenic response during fractionated radiotherapy develops in patients. Furthermore, it is important to determine whether this up-regulation can be inhibited by the administration of bevacizumab, a monoclonal antibody against VEGF. In this way an optimal dose schedule could be designed for the combination treatment of angiostatic drugs and radiotherapy.

Similar as described for tumour angiogenesis, radiotherapy has also been shown to prime the immune system for both adaptive and innate antitumour responses. With the emerging success of immunotherapy in the clinic it is thus vital to explore how fractionated irradiation affects immune response signalling.

Study objective

This study has 2 primary objectives:
1) To determine the time point of induction of VEGF expression in the tumour tissue of oesophagus carcinomas during chemoradiation.
2) To determine whether the tumour promoting effects of this induction of VEGF expression can be inhibited by administration of bevacizumab.

Study design

Multi centre, non-randomized, interventional pilot study

Intervention

Patients will undergo 2 extra endoscopic biopsies to collect tumour tissue. In addition, on one timepoint a blood samples will be collected. The time point of this biopsy and blood collection depends on the study cohort. The patients in the final cohort will receive bevacizumab (3mg/kg/wk) starting at the identified time point of induction. Bevacizumab administration will be discontinued 4 weeks before the surgical resection of the tumour.

Study burden and risks

Enrolment in this study implies that the patient will undergo 2 extra endoscopic biopsies of the oesophageal tumour and 1 extra venepuncture. As much as possible, we will try to collect the extra blood sample together with routine laboratory blood analysis. The biopsy may cause physical discomfort, which will be equal to the discomfort at the diagnostic biopsy. The extra biopsy will not give any additional risc factors for the patient, other than the biopsy at the diagnostic procedure.
The addition of bevacizumab (3mg/kg/wk) has been proven to be clinically well tolerable with low grade toxicities, when given together with the chemoradiation in esophageal cancer. If not well tolerated, the bevacizumab will be discontinued. Treatment of bevacizumab concurrent with chemoradiation is known to increase the risk of gastro-intestinal perforations. Although no data is available about the risk in esophageal cancer patients, the overall incidence is between 1-4%. Therefore extra attention will be paid to the clinical status of the patients treated with bevacizumab However, this study uses a lower dose of bevacizumab that normally used for cancer patients, which might reduce the risc of toxicities.
Results of this study will be used to design a following phase I/II clinical trial, to test an optimal schedule for the combination treatment of radiotherapy and angiostatic drugs.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081 HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

(1) Histological confirmation of adenocarcinoma of the oesophagus
(2) Patients that will receive standard chemoradiation treatment before surgery for oesophageal carcinoma
(3) Ability to give informed consent
(4) Age 18 years or older
(5) no prior therapy for oesophageal carcinoma

Exclusion criteria

(1) pregnancy
(2) Inflammation of the gastro-intestinal tract
(3) Brain metastasis
(4) Diastolic/ systolic Hypertension (>90/>140 mmHg), not responding to treatment
(5) Arterial thromboembolism in medical history
(6) Surgery within the month prior to start of bevacizumab treatment

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-02-2015
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-09-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-05-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2019
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	EUCTR2013-002563-25-NL
CCMO	NL45194.029.13