A phase I/II trial testing nelfinavir, an inhibitor of Akt signaling, in combination with preoperative chemoradiotherapy in patients with locally advanced rectal cancer

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The aim is to study safety and activity of nelfinavir, added to standard chemoradiotherapy (26x1.8 Gy and capecitabine 825 mg/m2 BID) in patients with locally advanced rectal cancer. Furthermore analysis of the effect of nelfinavir combined with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON31565

Source
ToetsingOnline

Brief title
nelfinavir phase I/II rectum study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: MAASTRO clinic
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: chemoradiation, locally advanced rectal cancer, nelfinavir, radiosensitivity

Outcome measures

Primary outcome

Phase I: incidence of any grade 3 or higher non-hematological or grade 4 or

higher hematological toxicity and incidence of grade 4 or higher postoperative

toxicity within 30 days post-surgery

Phase II: the rate of pathological complete remission (pCR)

Secondary outcome

- Progression free and overall survival

- Local and distant recurrence rate

- Metabolic response rate on CT-PET at time of surgery

- Phosphorylation of Akt in the tumor at different time points

- Tumor perfusion assessed by dynamic CT-scan

Study description

Background summary

The incidence of colorectal cancer is high in The Netherlands. The treatment of rectal cancer has changed importantly over the last decades. At the moment preoperative radiotherapy is a cornerstone in rectal cancer treatment. In patients with locally advanced tumors, combined treatment using capecitabine and radiotherapy in 6 weeks, followed by surgical resection 6-8 weeks after completion of chemoradiation. This combined modality treatment can cause tumorregression, resulting in downsizing and downstaging. In 10-15% of cases

this treatment results in a pathological complete response (pCR). There is a correlation between the degree of response and the chance to develop a local recurrence. Therefore, it is important to develop new combined treatments resulting in higher persentages of pCR, without an important increase of toxicity. Preclinical work shows that nelfinavir, a protease inhibitor used in the treatment of HIV, increases the radiosensitivity of tumor cells without sensitization of normal tissues to radiation. For that reason, no extra toxicity is expected by adding nelfinavir to the combined chemoradiation treatment.

Study objective

The aim is to study safety and activity of nelfinavir, added to standard chemoradiotherapy (26x1.8 Gy and capecitabine 825 mg/m2 BID) in patients with locally advanced rectal cancer. Furthermore analysis of the effect of nelfinavir combined with chemoradiation on tumor tissue will be studied.

Study design

This is an open label, single-center phase I/II trial. During phase I the toxicity of 2 dose levels will be studied (750 mg BID and 1250 mg BID). During phase II the activity of nelfinavir in combination with capecitabine and radiotherapy will be studied, using the MTD from phase I. With respect to translational research, phosphporylation of Akt in monocytes and tumorcells will be measured at different timepoints during treatment. Furthermore, dynamic CT-PET scans will be obtained at different time points to get an impression of changes in SUV and perfusion during treatment and to correlate these changes with pathological response.

Intervention

Phase I:
- take nelfinavir tablets (minimum 6, maximum 10) starting 7 days before start of chemoradiotherapy, for 35 days
- day 7 and week 2-4-6 bloodsamples

Phase II:
- take XXXX (to define) nelfinavir tablets starting 7 days before start of chemoradiotherapy, for 35 days
- day 7 and week 2-4-6 bloodsamples
- day 7 biopsy
- day 7-14-21 and week 13 PET-CT

Study burden and risks

No major toxicity is expected from the addition of nelfinavir to the standard

chemoradotherapy. The most common side effect of nelfinavir is diarrhoea. Extra scans, blood samples and biopsy demands extra time. For the extra scans, the injection of 18FDG and IV contrast is necessary. To take an extra biopsy, an extra sigmoidoscopy must be performed.

Contacts

Public
MAASTRO clinic

dr. Tanslaan 12
6229 ET Maastricht
NL
Scientific
MAASTRO clinic

dr. Tanslaan 12
6229 ET Maastricht
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Histologically proven adenocarcinoma of the rectum (tumor <15cm from anal verge)
• Age >= 18 years
• UICC T3-4 N0-2 M0
• WHO performance status 0-2
• Less than 10 % weight loss the last 6 months
• No recent (< 3 months) severe cardiac disease (arrhythmia, congestive heart failure,

infarction)
• Serum bilirubin * 3x normal
• ASAT and ALAT * 2,5x normal
• Creatinin clearance >50 ml/min
• Willing and able to comply with the study prescriptions
• No history of prior pelvic radiotherapy
• No known HIV infection
• No hemophilia
• No concurrent medication that is metabolized by the CYP3A4 isoenzyme (calcium channel blockers, antifungal agents, macrolide antibiotics, gastrointestinal prokinetics, terfenadin, midazolam)
• Statins should be stopped (except pravastatin and fluvastatin),
• No concurrent use of St. John*s Wort (Hypericum perforatum)
• Women should not be pregnant or lactating
• Being willing and able to undergo one extra biopsy
• Have given written informed consent before patient registration

Exclusion criteria

the opposite of the above

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-09-2008
Enrollment:	61
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Viracept
Generic name:	nelfinavir
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Xeloda 825 mg/m2 BID
Generic name:	Capecitabine 825 mg/m2 BID
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	26-07-2007
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-08-2008
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-09-2008
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-01-2009
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2007000728-41-NL
CCMO	NL16750.068.07