Phase 1 study of cisplatin/hyperthermia/lapatinib in patients with previously irradiated recurrent carcinoma of the uterine cervix.

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This phase I study aims to define the MTD of the combination of cisplatin/hyperthermia/lapatinib, to confirm that the 2 agents combined with hyperthermia can be administered safely, and to recommend a dose for further clinical studies.

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

Summary

ID

NL-OMON36858

Source
ToetsingOnline

Brief title
Cisplatin/Lapatinib/hyperthermia

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
cervical cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Glaxo Smith Kline

Intervention

Keyword: cervical carcinoma, chemotherapy, EGFR, hyperthermia

Outcome measures

Primary outcome

To establish a MTD of lapatinib in combination with a standard dose of

cisplatin (weekly 70 mg/m2) and local hyperthermia and to recommend a dose for

further clinical studies

Secondary outcome

To assess safety and tolerability of lapatinib in combination with cisplatin

and hyperthermia

To describe the activity of lapatinib in combination with cisplatin and

hyperthermia in patients with previously irradiated recurrent carcinoma of the

uterine cervix

Translational research: HER1/HER2 tumour tissue expression, Circulating

endothelial cells (CEC*s), Skin-biopsy: activation of HER1/2 mediated pathways

prior to and once during treatment.

Study description

Background summary

The combination of weekly systemic cisplatin and locoregional hyperthermia is considered standard treatment in patients with local pelvic relapse from previously irradiated carcinoma of the uterine cervix. In addition, this

combination of cisplatin and locoregional hyperthermia is used in patients with distant metastases, who urgently need pain control from local relapse (Br J Cancer; 1999; 80: 1387-91). The overall response rate of this treatment regimen is about 50%, with a median duration of response of 6 months. Epidermal growth factor receptor (EGFR) overexpression is negatively associated with overall survival in patients with cancer of the uterine cervix (Gynecol Oncol; 2002; 87: 84-9, Int J Radiat Oncol Biol Phys; 2003; 56: 922-8). In addition, preclinical studies have shown that a combination of cisplatin and an EGFR-inhibitor acts synergistically (Anticancer Res; 2003; 23: 2577-83). Preliminary safety data show that lapatinib can be safely combined with cisplatin in patients undergoing chemoradiation because of head/neck carcinoma, with acceptable toxicity.

Study objective

This phase I study aims to define the MTD of the combination of cisplatin/hyperthermia/lapatinib, to confirm that the 2 agents combined with hyperthermia can be administered safely, and to recommend a dose for further clinical studies.

Study design

This is a Phase I, open-label, non-randomized, dose-escalation trial in sequential cohorts of patients. Cohorts of 3 patients (to be expanded to 6 if 1 DLT is observed among the 3 patients) will be sequentially treated with progressively higher dose levels of once daily lapatinib (1000 mg and 1500 mg) in combination with weekly cisplatin 70 mg/m2 and locoregional hyperthermia. In case of a DLT at the dose level of 1000 mg, the dose will be lowered to 750 mg (=DL -1).The duration of the DLT period is 6 weeks.
In case of 2 DLTs at dose level 750 mg, the dose of lapatinib will be reduced to 500 mg (=DL -2).

Intervention

Weekly hyperthermia combined with weekly cisplatin intravenously given at a dose of 70 mg/m2 in combination with escalating dose of daily continuous lapatinib for a total treatment period of 6 weeks.

Study burden and risks

The burden may be, if the patient agrees, the procedure of twice a skinbiopsy and once a prolonged stay in the hospital for one day. The riscs may be additional toxicity of the combination of lapatinib and cisplatin with hyperthermia.

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 pelvic recurrence of cervical cancer in previously irradiated area (with or without distant metastases), not amendable for surgery or additional radiotherapy, for which treatment with cisplatin/hyperthermia is indicated.
Age >= 18 years.
WHO performance of 0-1 and a predicted life expectancy of at least more than 12 weeks.
Adequate liver-, kidney- and bone marrow function
Left ventricular ejection fraction (LVEF) within normal range or above 50% based on MUGA/ECHO
Able to swallow and retain oral medication
Before patient registration, written informed consent must be given

Exclusion criteria

· Prior systemic chemotherapy for recurrent tumour
· Prior treatment with lapatinib
· Pacemaker
· Artificial hip
· Pre-existing motor or sensory neurotoxicity greater than WHO grade 1
· Untreated leptomeningeal or brain metastases.
· Class II, III or IV heart failure as defined by the NYHA functional classification system
· History of congestive heart failuire, clinically significant valvular disease, or poorly controlled hypertension
· Arterial or venous thrombosis
· Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to lapatinib
· Any major surgery, hormonal therapy (other than replacement), chemotherapy or radiotherapy, immunotherapy or other investigational agent within the last 28 days and/or not recovered from prior therapy within the last 28 days have to wait 42 days before starting therapy.)
· History of malabsorption syndrome, disease significantly affecting gastrointestinal function or major resection of the stomach or small bowel that could affect absorption, distribution, metabolism or excretion of study drugs
· Any unresolved bowel obstruction or diarrhea
· Other concurrent serious disease, such as severe pulmonary conditions
· Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol
· Is on any CYP3A4 inducing or inhibiting medication or requires any of these medications during treatment with lapatinib
· Has significant QTc prolongation (QTc interval greater than or equal to 480 msec) AND a prior history of cardiovascular disease, arrhythmias, or significant ECG abnormalities

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):	10-04-2009
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tykerb
Generic name:	lapatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-08-2010
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2008-005083-13-NL
CCMO	NL24464.078.08

Study results

Date completed:	04-04-2012
Results posted:	18-07-2019

First publication
04-01-2015