Phase I study of Cisplatin, gemcitabin (+ paclitaxel) and lapatinib as first line treatment in advanced/metastatic urothelial cancer

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

Summary

ID

NL-OMON31194

Source
ToetsingOnline

Brief title
EORTC protocol 30061

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
urothelial 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: EORTC en Glaxo Smith Kline verzorgt de lapatinib.,GlaxoSmithKline

Intervention

Keyword: Advanced metastatic, Lapatinib, Phase I, Urothelial cancer

Outcome measures

Primary outcome

To identify the maximum tolerated dose (MTD) of Lapatinib in combination with cisplatin/gemcitabine and cisplatin/gemcitabine/paclitaxel based on the documentation of the acute dose limiting toxicity (DLT) in cycle 1.

Secondary outcome

- To determine the pharmacokinetic profile of Lapatinib in combination with cisplatin/gemcitabine and cisplatin/gemcitabine/paclitaxel

- To assess the anti-tumor activity according to RECIST, in those patients with measurable disease

- To explore the patient population by determination of intra-tumoral expression levels of relevant biomarkers from tumor tissue: three Erb/EGFR family members (HER1, HER2,HER3, HER4), AKT (58kDa serine/threonine protein kinase), TUNEL, p53 , MAPK and Insulin-like growth factor-1 (IGF-1R) and potentially other signalling pathways likeVEGF together with biomarkers that are downstream of these receptors.

Study description

Background summary

Urothelial cancer is the 5th most common malignancy in Europe. Transitional cell carcinoma (TCC) comprises 90-95% of the urothelial tumors in Europe. Most of these tumors are superficial and although frequently recurring, of good prognosis. However, in patients diagnosed with muscle invasive TCC, only 30-60% can be cured with adequate local treatment. Others will develop local relapse or distant metastasis.

Despite the advances in local and systemic therapy, metastatic transitional cell carcinoma (TCC) remains a largely incurable disease. The overall response rate to combination chemotherapy with modern agents is on the order of 60-70%, but median survival remains less than two years with a five year survival of approximately 10% (Ref. 1). The EORTC has recently completed a trial of gemcitabine and cisplatin +/- paclitaxel establishing that this triplet can be given safely in the cooperative group setting. Whether the triplet results in improved survival is as of yet unknown.

Insights into the biology of malignant transformation and growth suggest novel targets for therapy which may improve treatment results (Ref. 2).
HER1 is overexpressed in around 70% of bladder cancers. Combined expression of HER1 and HER2 is found in around 34% of the tumors and 90 % of the patients have at least one of these receptors overexpressed. Dual HER1/HER2 inhibition is therefore an attractive therapeutic strategy for epithelial tumors including bladder cancer, as ligand-induced HER2/HER1 heterodimerization triggers potent proliferative and survival signals.

Lapatinib is a small molecule inhibitor of tyrosine kinase activity of both HER1 and HER2. It has been shown that Lapatinib, potently inhibits both HER1 and HER2 tyrosine kinases leading to growth arrest and/or apoptosis in HER1 and HER2-dependent tumor cell lines. Lapatinib markedly reduced tyrosine phosphorylation of HER1 and HER2, and inhibited activation of Erk1/2 and AKT, downstream effectors of proliferation and cell survival, respectively.
Inhibition of activated AKT in
HER1 or HER2-dependent tumors by Lapatinib may lead to tumor regressions and may enhance the anti-tumor activity of chemotherapeutics since constitutive activation of AKT has been linked to chemo-resistance.

At ASCO in 2006 some clinical studies were presented which included Lapatinib. In renal cell cancer a prolongation of overall survival was observed in Lapatinib treated patients compared to hormone therapy in advanced renal cell cancer with overexpressed EGFR who had failed prior therapy (Ref. 7). No responses were seen in biliary cancer but 2 out of 17 patients with hepatocellular carcinoma obtained PR (Ref. 8). Little activity was seen in head

and neck cancer.

Novel, biologically based cancer therapies with clinically significant anti-tumor activity, accompanied by significant disease-related symptom improvement in bladder cancer, would fulfill an unmet medical need. As many cancer patients bear tumors that express both HER1 and HER2, a dual inhibitor of the HER receptor family, such as Lapatinib, may be more effective than a drug that specifically inhibits either receptor. This study is being conducted to evaluate the pharmacokinetic
profile and toxicity of Lapatinib in combination with cisplatin/gemcitabine and cisplatin/gemcitabine/paclitaxel and to explore anti-tumor activity of the combinations.

Study objective

The primary objective of this trial is to recommend a dose of Lapatinib in combination with Gemcitabine, Cisplatin and possibly Paclitaxel. In order to achieve this, the study will first determine the maximum tolerated dose (MTD) based on the documentation of the acute dose limiting toxicity (DLT) at cycle 1.

Secondary objectives are:
- to determine any relationship between the drug exposure and adverse events,
- to assess the antitumor activity and
- to explore the intra-tumoral expression levels of relevant biomarkers in patients.

Study design

This is a Phase I, multinational, open-label, dose-escalation study of Lapatinib in combination with Gemcitabine and Cisplatin (and eventually Paclitaxel) in patients with advanced or metastatic urothelial cancer.

The study will be conducted in 5 centers by the Genito-Urinary Tract Cancer Group of the European Organisation for Research and Treatment of Cancer (EORTC). Patients will be registered at the EORTC Data Center prior to start the treatment, and after verification of their eligibility.
Eligible patients will receive the combined treatment as described in chapter 5, page 22-24.

The doses of Gemcitabine and Cisplatin are fixed and the dose of Lapatinib will be escalated.
Design: 3+3 scheme with 3 patients per dose level and up to 6 patients in case of DLTs.

Intervention

Two combinations will be investigated in this trial:

1.Gemcitabine/Cisplatin/Lapatinib (q4wks)
Gemcitabine: 1000 mg/m² days 1, 8, 15
Cisplatin: 70 mg/m² day 2
Lapatinib: d1-28, 750 mg/d to 1500 mg/d (dose escalation)

2. Gemcitabine/Cisplatin/Lapatinib/Paclitaxel (q3wks)
Gemcitabine: 1000 mg/m² days 1, 8
Cisplatin: 70 mg/m² day 1
Lapatinib: d1-21, dose below recommended dose in combination with Gem-Cis
Paclitaxel: 80 mg/m² days 1, 8

Study burden and risks

Extra burden is the physical examination, ECG, ejection fraction (page 33/101), venapunction and possible side effects.

Contacts

Public
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounierlaan 83/11
1200 Brussel
BE
Scientific
European Organisation for Research in Treatment of Cancer (EORTC)

Avenue E. Mounierlaan 83/11
1200 Brussel
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically proven TCC of the urothelial tract in patients who overexpress HER1 and/or HER2 (IHC 2/3+ FISH/CISH +)
- Metastatic or locally advanced disease with involvement of at least one target not in previously irradiated fields
- Tissue from the primary or metastatic site must be available for biomarker status determination
- Measurable disease according to RECIST
- Normal bone marrow, renal, hepatic and cardiac functions

Exclusion criteria

- No prior chemotherapy for metastatic disease.
- No radiotherapy within the last 4 weeks before inclusion
- Drugs which are inducers or inhibitors of CYP3A4 are prohibited

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):	01-10-2007
Enrollment:	12

Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Lapatinib
Generic name:	lapatinib ditosylate

Ethics review

Approved WMO Date:	22-08-2007
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-11-2008
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-01-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-09-2011
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	EUCTR2006-002976-16-NL
CCMO	NL18586.091.07