Phase I study of Gemcitabine plus Lapatinib (GW572016) in women with advanced breast cancer

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Primary objective: To evaluate the safety of Gemcitabine and Lapatinib in combination for the treatment of advanced breast cancer.Secondary objectives: Assessment of the effect of Gemcitabine and Lapatinib on the pharmacokinetics of each other and...

Ethical review	Approved WMO
Status	Pending
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON30513

Source
ToetsingOnline

Brief title
N06GLB

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Farmaceutische industrie,GlaxoSmithKline

Intervention

Keyword: Brest cancer, Gemcitabine, Lapatinib, Phase I

Outcome measures

Primary outcome

Safety Outcome Measures: Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0 (van 10 june 2003). Safety assessments will be based on medical review of adverse events reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests throughout the conduct of the study.

Secondary outcome

Pharmacokinetic Measures: Pharmacokinetic parameters (Cmax, Tmax, AUC(inf) en T1/2) will be derived froma plasma concentration versus time data.

Tumor Response Outcome Measures: Tumor response will be obtained from all patients with measurable lesions, using the RECIST criteria. The assessments will be made every two cycles (after cycle 2, 4, 6 etc.) or more frequently if indicated. Furthermore, a response is considered confirmed if it is noted on two examinations at least four weeks apart.

Study description

Background summary

Gemcitabine has a broad range of activity and favourable toxicity profile. In phase I and II trials gemcitabine mono-therapy, or in combination, has been shown to be active and well tolerated in both chemotherapy naïve and pre-treated breast cancer patients. As mono-therapy gemcitabine gives response rate ranging from 14 - 37% and 12 - 30% in fist and second line treatment, respectively. Studies have shown that gemcitabine can safely be combined with

paclitaxel, docetaxel, vinorelbine, cisplatin, carboplatin and capecitabine in breast cancer patients. Furthermore, phase III trials have confirmed the activity of gemcitabine in combination with capecitabine.
In preclinical studies gemcitabine and trastuzumab has been shown to act synergistically in Her2/neu overexpressing breast cancer cell lines.
Gemcitabine plus trastuzumab has been evaluated in a small phase II study in Her2/neu positive breast cancer patients showing that this combination is both effective and tolerable in previously treated breast cancer patients.
Lapatinib has been shown to be active as monotherapy and in combination with various chemotherapeutic agents in patients with advanced Her2/neu overexpressing breast cancer previously treated with both chemotherapy and trastuzumab. Developing a lapatinib and gemcitabine combination gives us the possibility to administer two active agents with possible synergistic activity and favourable toxicity profile, to women with advanced breast cancer, in an attractive treatment schedule.

Study objective

Primary objective: To evaluate the safety of Gemcitabine and Lapatinib in combination for the treatment of advanced breast cancer.
Secondary objectives: Assessment of the effect of Gemcitabine and Lapatinib on the pharmacokinetics of each other and assessment of the efficacy of Gemcitabine and Lapatinib in patients with advanced breast cancer.

Study design

This is a phase I, open label study of Gemcitabine in combination with Lapatinib in patients with advanced breast cancer.
The recommended dose of Lapatinib and Gemcitabine in combination will be determined by dose adjustment. Patients will be treated in cohorts of three per dose level. Each cycle consists of 4 weeks of therapy. The starting doses will be 750 mg of Lapatinib, given as tablets once daily on day 1 - 28, and Gemcitabine, 750 mg/m2, given as a 30 min. intravenous infusion on day 1, 8 and 15, repeated 4 weekly. Further dose escalation (see table below) will be performed according to the toxicity and pharmacokinetic profile observed at prior dose levels.
Previously, Gemcitabine 1000 mg/m2 on day 1, 8 and 15 (q 4 weeks) plus Lapatinib 1500 mg/day continue has been shown to be safe in patients with advanced pancreatic cancer.
Should one patient of the first three experience dose-limiting toxicity (DLT), the number of patients treated at this dose level will be expanded to maximally six. Provided none of the additional three patients experience DLT, further dose escalation will continue.
Dose escalation will continue until a dose is reached at which more than one of the expanded cohort of six patients experience DLT during their first cycle of the combination (maximum tolerated dose, MTD).

In case of MTD and determination of optimal treatment regimen 6 - 12 additional patients will be entered at this dose level for PK analysis.
Intra-patient dose escalation will be permitted across only one dose level of both Gemcitabine and Lapatinib.

Dose escalation table:
Cohort 1: Gemcitabine 750 mg/m2 + Lapatinib 750 mg OD continue
Cohort 2: Gemcitabine 1000 mg/m2 + Lapatinib 750 mg OD continue
Cohort 3: Gemcitabine 1000 mg/m2 + Lapatinib 1000 mg OD continue
Cohort 4: Gemcitabine 1000 mg/m2 + Lapatinib 1250 mg OD continue
Cohort 5: Gemcitabine 1000 mg/m2 + Lapatinib 1500 mg OD continue
Cohort 6: Gemcitabine 1250 mg/m2 + Lapatinib 1500 mg OD continue

Blood samples for pharmacokinetics of Gemcitabine and Lapatinib will be collected over 24 hours on day 1 and 2 of the first cycle (hospital admission) and over 1 hour on day 8, 15 and 29 (outpatient care).

Intervention

Chemotherapy with Gemcitabine and Lapatinib combination according to the following schedule:

Gemcitabine infusion on day 1, 8 and 15 in a cycle of 28 days.
Lapatinib tablets once daily continue day 1 - 28 in a cycle of 28 days.

Study burden and risks

Patients will undergo pharmacokinetic analyses during 12 hours on day 1 of the first cycle. Furthermore, one additional blood sample will be collected on day 2, 8 and 15 of the first cycle and on day 1 of cycle 2. Thereafter visits are scheduled once weekly before each Gemcitabine administration on day 1, 8 and 15 of a 4 week schedule. Anticipated risks are related to the experimental study medication and listed in the patient information sheet.

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

All patients who are considered for palliative Gemcitabine chemotherapy for advanced breast cancer.
Furthermore:
1. > 18 years
2. Performance status: WHO 0 - 2
3. Life expectancy > 3 months
4. Histological or cytological proof of breast cancer
5. Evaluable or measurable disease according to RECIST criteria
6. Previous chemotherapy with an anthracycline and a taxane.
7. Previous Trastuzumab (Herceptin®) in case of Her2/neu overexpression (IHC) or gene amplification (FISH/CISH)
8. No radiotherapy for at least 2 weeks prior to study entry
9. Minimal acceptable safety laboratory values
a. ANC of >= 1.5 × 109/l
b. Platelet count of >= 100 × 109/l
c. Haemoglobin level of >= 10 g/dl (>= 6.2 mmol/l)
(prior transfusion is permitted)
d. Hepatic function as defined by serum bilirubin <= 1.5 times the upper limit of normal, ALT and AST <= 2.5 times the upper limit of normal.
e. Renal function as defined by serum creatinine <= 1.5 times upper limit of normal or creatinine clearance >= 50 ml/min (by Cockcroft-Gault formula).
10. Cardiac ejection fraction (LVEF) within the institutional range of normal as measured by echocardiogram or MUGA scan (i.e. > 50%). Baseline and on treatment scans should be performed using the same modality.

11. Able to swallow and retain oral medication
12. Written informed consent

Exclusion criteria

1. More than three previous courses of chemotherapy including adjuvant chemotherapy
2. Patients who have received a cumulative dose of adriamycine more than 360 mg/m2 or a cumulative dose of epirubicine more than 600 mg/m2.
3. Symptomatic CNS metastases.
4. Previous investigational cytotoxic or biological treatment for malignant disease within 30 days before the start of the study.
5. Any treatment with non-oncological investigational drugs within 30 days before the start of the study
6. Concomitant requirement for medication classified as CYP3A4 inducers or inhibitors.
7. Patients using medications or substances known to affect, or with the potential to affect the activity or pharmacokinetics of Lapatinib.
8. Treatment within one week before the start of the study with any of the following: terfenadine, cisapride, cyclosporin, tacrolimus, theophylline, diazepam, sulphonylurea hypoglycaemics, phenytoin, or carbamazepine.
9. Uncontrolled infections.
10. All herbal (alternative) medicines are excluded, but multivitamins are allowed.
11. Pregnancy or breast feeding (all women of childbearing potential must have a pregnancy test before inclusion in the study; post-menopausal women must have amenorrhoea for at least 12 months). Female patients must use adequate contraceptive protection.
12. HIV-positive patients receiving combination anti-retroviral therapy are excluded from the study because of possible pharmacokinetic interactions with Lapatinib.
13. Clinically significant cardiac impairment or unstable ischaemic heart disease including a myocardial infarction (< 3 months of study entry)
14. History of alcoholism, drug addiction, or any psychiatric or psychological condition which in the opinion of the investigator would impair study compliance
15. Malabsorption syndrome or other condition which may affect absorption of Lapatinib.
16. Concurrent or previous malignancy of a different tumour type within five years of starting the study except for adequately treated non-melanoma skin cancer or cervical intraepithelial neoplasia
17. Patients who have had previous treatment with Lapatinib.
18. Legal incapacity

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2007
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tycerb
Generic name:	Lapatinib

Ethics review

Approved WMO

Date:	12-03-2007
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	18-02-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	14-10-2008
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2006-003778-82-NL
CCMO	NL14053.031.07