Phase I study of gemcitabine and carboplatin plus sorafenib in patients with advanced solid tumors

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primary • To determinne the safety and tolerability of sorafenib when administered in combination with gemcitabine and carboplatin.• To determine the maximal tolerated dose (MTD), dose limiting toxicity (DLT) and optimal treatment schedule of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON31053

Source
ToetsingOnline

Brief title
Phase I study Gemcitabine and carboplatin plus sorafenib

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced solid tumors, Cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Carboplatine, Gemcitabine, Phase 1, Sorafenib

Outcome measures

Primary outcome

Safety and tolerability endpoints will consist of the evaluation of adverse events (AE*s), serious adverse events (SAE*s) and all clinically significant changes in clinical laboratory values.

A dose regimen resulting in no more than 1 out of 6 patients with DLT will be estimated and defined as the optimally tolerated regimen.

Secondary outcome

Pharmacokinetic endpoints will consist of parameters such as AUC, Css, Cmax, tmax and t1/2 of i.v. carboplatin and Gemcitabine and oral Sorafenib in combination.

Assessment (according to RECIST criteria) of antitumor activity will be obtained every 2 cycles (6 weeks) and will be recorded as complete response, partial response, stable disease or progressive disease

Study description

Background summary

Intravenously administered gemcitabine is the drug of choice for pancreatic cancer as single-agent therapy and for non-small cell lung cancer (NSCLC) and bladder cancer as combination therapy with cisplatin. It has also demonstrated activity, either as a single-agent or in combination, in several other tumor types, such as bladder cancer, breast cancer, testicular cancer, sarcoma and ovarian cancer. As carboplatin has a more favourable nonhematologic toxicity profile than cisplatin, combinations of carboplatin or cisplatin with gemcitabine have been compared in randomized phase II and III studies in NSCLC,

bladder cancer and pancreatic cancer. Carboplatin and gemcitabine combination chemotherapy has been shown to be very active in relapsed ovarian cancer patients in a phase III study comparing single agent carboplatin with the combination of carboplatin and gemcitabine.
A recently presented phase I study of the combination of gemcitabine plus sorafenib in patients with advanced solid tumors identified gemcitabine 1000 mg/m2 weekly x 7 followed by 1 rest week plus sorafenib 400 mg BID as the optimal treatment schedule. In this phase I study antitumor activity was observed in patients with pancreatic and ovarian cancer.
In the light of known synergy between other targeted treatments and diverse chemotherapeutic agents the combination of Gemcitabine, carboplatin and sorafenib might be an efficacious treatment modality for many solid tumors like lung cancer, bladder cancer, pancreatic cancer and ovarian cancer.
Developing a Gemcitabine, carboplatin and sorafenib combination gives us the possibility to administer three active agents with possible synergistic activity and favourable toxicity profile, to patients with advanced solid tumors, in an attractive treatment schedule.

Study objective

primary
• To determinne the safety and tolerability of sorafenib when administered in combination with gemcitabine and carboplatin.
• To determine the maximal tolerated dose (MTD), dose limiting toxicity (DLT) and optimal treatment schedule of Gemcitabine and carboplatin plus Sorafenib in patients with advanced solid tumors.

secundary
• To explore the pharmacokinetic and pharmacodynamic profile of systemic exposure of Gemcitabine, carboplatin and Sorafenib in combination.
• To assess the clinical activity of gemcitabine and carboplatin in combination with sorafenib in patients with advanced solid tumors.

Study design

This is a phase I, single centre, open-label, non-randomized study to define the safety profile, pharmacokinetics and maximum tolerated dose (MTD) of sorafenib in a continuous dosing schedule in combination with gemcitabine and carboplatin in patients with advanced solid tumors. Other objectives include determination of optimal treatment schedule, pharmacokinetic profile and efficacy of the combination. The number of subjects to be included is expected to be up to 28 evaluable patients in several cohorts of 3 - 6 patients per cohort. The cohort with the safest and most feasible combination of gemcitabine, carboplatin and sorafenib will be expanded with 6-12 patients. Intra-patient dose escalation will be permitted across only one dose level of all study drugs.

Intervention

Gemcitabine, carboplatin and sorafenib in a cycle of 3 weeks.

Gemcitabine infusion every 1st and 8th day
Carboplatin infusion every 1st day
Sorafenib intake twice daily continuous.

Study burden and risks

Anticipated risks are related to the experimental study medication and are listen 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

Patients with progressive advanced solid tumor who are considered for palliative gemcitabine plus carboplatinb combination chemotherapy.
Furthermore:
• > 18 years.
• Performance: WHO 0 - 2.
• Life expectancy > 3 months.
• Histological or cytological proof of malignancy.
• Measurable disease according to RECIST criteria.
• Minimal acceptable safety laboratory values.
o ANC of >= 1.5 × 109/L
o Platelet count of >= 100 × 109/L
o Haemoglobin level of >= 10 g/dL (>= 6.2 mmol/L)
(prior transfusion is permitted)
o Hepatic function as defined by serum bilirubin <= 1.25 times the upper limit of normal (ULN), ALT and AST <= 2.5 times the ULN, except if liver metastases then ALAT and ASAT < 5 times the ULN.
o Renal function as defined by serum creatinine <= 1.25 times ULN or creatinine clearance >= 50 ml/min (by Cockcroft-Gault formula).
• Able to swallow and retain oral medication.
• Written informed consent.
• Willingness to use a medically approved method of contraception
• Caution is recommended when administering sorafenib with inhibitors of the CYP3A4 family (eg, ketoconazole, itraconazole, erythromycin, clarithromycin, warfarine).

Exclusion criteria

• Previous investigational cytotoxic or biological treatment for malignant disease within 30 days before the start of the study.
• Any treatment with non-oncological investigational drugs within 30 days before the start of the study.
• Radiotherapy within 2 weeks prior to study entry.
• Major surgery within 4 weeks prior to study treatment.
• Patients using medications or substances known to affect, or with the potential to affect the activity or pharmacokinetics of sorafenib.
• 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). All patients must use adequate contraceptive protection.
• History of alcoholism, drug addiction, or any psychiatric or psychological condition, which in the opinion of the investigator would impair study compliance.
• 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

• Legal incapacity
• Uncontrolled or poorly controlled hypertension (Systolic blood pressure >= 150 mmHg, diastolic blood pressure >= 90 mmHg). Initiation or adjustment of blood pressure medications is permitted prior to study treatment provided that 3 consecutive BP readings are less than 150/90 mmHg, each separated by at least 24 hours
• History of malabsorption syndrome or other disease that could significantly affect absorption of drugs
• Systemic steroids within 2 weeks prior to study treatment
• Myocardial infarction or cerebrovascular accident (CVA) within 6 months prior to study treatment
• Congestive heart failure requiring medication.
• Symptomatic brain metastases.
• Hepatic dysfunction
• Uncontrolled infections.
• Known human immunodeficiency virus (HIV) infection
• Known chronic or acute viral hepatitis
• Patients who have known hypersensitivity to the study medication

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2007
Enrollment:	28
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Carbosin
Generic name:	Carboplatin

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Nexavar
Generic name:	Sorafenib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-08-2007
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-09-2007
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-10-2008
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2010
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2007-004129-75-NL
CCMO	NL19076.031.07