A phase II, randomized, placebo controlled study to evaluate the efficacy of the combination of gemcitabine, erlotinib and metformin in patients with locally advanced and metastastatic pancreatic cancer

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

Summary

ID

NL-OMON34831

Source
ToetsingOnline

Brief title
metformin and pancreatic cancer

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic pancreatic cancer

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: MAPK pathway, metformin, pancreatic cancer, PI3K/Akt pathway

Outcome measures

Primary outcome

Survival after 6 months.

Secondary outcome

-Progression free survival

-Objective response rate

-Toxicity profile

-Pharmacodynamics: biomarkers in blood and tumour tissue

Study description

Background summary

Pancreatic cancer patients have one of the worst prognoses among all cancer types with a 5 year survival rate of less than 5%. Despite significant changes during the last decade in our molecular knowledge on this disease, the prognosis and management of pancreatic cancer have remained unchanged. With the advances in molecular biology, newer biologic agents such as erlotinib, cetuximab and bevacizumab are adding some benefit to the conventional cytotoxic agents. Unfortunately, these agents all failed to show any significant superiority over gemcitabine except the combination of erlotinib plus gemcitabine; however, the clinical impact of this combination remains controversial until now.
There is a growing body of literature suggesting that type 2 diabetes mellitus (DM) may be associated with the development of pancreatic cancer, but this association is complex. Because various DM medications can affect directly the

key factors mediating the association between DM and pancreatic cancer, understanding the effect of anti-diabetic therapies on pancreatic cancer is a critical step in fully characterizing the role of type 2 DM in the development of pancreatic cancer. Indeed, two epidemiologic studies have found that diabetic patients treated with metformin were less likely to develop cancer, but those treated with insulin were more likely to die of various kinds cancer.
Not only does metformin ameliorate hyperglycemia and hyperinsulinemia, both of which are associated with the adverse impact of DM on cancer, metformin also has direct metabolic effects through activation of adenosine monophosphate-activated protein kinase (AMPK). AMPK regulates many metabolic enzymes and also inhibits the mammalian target of ramamycin (mTOR) pathway via phosphorylation and stabilization of the tumor suppressor gene TSC2. But there is an intensive cross-talk between various pathways. Inhibition of the phosphoinositide 3-kinase (PI3K)/Akt pathway, of which mTOR is one of the effector proteins, for instance may result in escape via the mitogen-activated protein kinase (MAPK) pathway and vice versa. Indeed, epidermal growth factor receptor (EGFR) activation leads to activation of the MAPK pathway and the PI3K pathway. Thus, since it is clear that blocking one pathway will not always be sufficient to produce a response in the presence of other activated pathways, the best change of success will be realized when using a combination of agents that inhibit separate pathways known to be critical to the survival of the tumour. In line with these observations, combining a small molecule against the EGFR and inhibition of the PI3K pathway by metformin might account for potential candidates of the above combinatorial approach. Therefore, in this study, we want to determine the activity and safety of concurrent interruption of the MAPK and PI3K pathways by the EGFR tyrosine kinase inhibitor erlotinb and metformin, combined with gemcitabine in patients with metatastatic pancreatic cancer.

Study objective

In this study we want to determine the activity and safety of concurrent interruption of the MAPK and PI3K pathways by the EGFR tyrosine kinase inhibitor erlotinb and metformin, combined with gemcitabine in patients with metatastatic pancreatic cancer.

Study design

This is a phase II randomized, placebo controlled study. Eligible subjects will be randomized to treatment with gemcitabine and erlotinib or gemcitabine, erlotinib and metformin or placebo.

Intervention

Gemcitabine at a dose of 1000 mg/m2 (iv, 30 minutes) will be given weekly, for

3 weeks, followed by one week treatment holiday.
Erlotinib will be administered at a daily dose of 100 mg at least one hour before or 2 hours after the ingestion of food.
Metformin/ placebo will be administered at a dose of 500 mg twice daily. If well tolerated the dose will be increased to 1000 mg twice daily in the second week.

Study burden and risks

Each cycle contains 4 weeks, in which the patients take erlotinib and metformin/ placebo daily. Gemcitabine will be administred via an infusion pump weekly, during 3 weeks followed by one week treatment holiday. At various days during treatment the patient will come to the hospital for blood investigations and evaluation of the toxicity profile. After 3 cycles (12 weeks) during the treatment fase a scan will be performed to establish response.
Gemcitabine has been used in a wide variety of malignancies, both as single agent and in combination with other cytotoxic drugs. Myelosuppression is the principal dose-limiting toxicity. Side effects that appear frequently (>10%) are oedema, neuropathy, fever, flu-like symptoms and somnolence. Dermatologic side effects are rash, alopecia and pruritus. Gastrointestinal: nausea/vomiting, constipation, diarrhoea and stomatitis. As written before, myelosuppression is the dose limiting toxicity. Finally, liver function disturbance can occur.
Erlotinib is a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. Side effects that appear frequently (>10%) are fatigue and dermatologic toxicity (e.g rash, dry skin and pruritus), diarrhoea, nausea and stomatitis. Other side effects are pneumonitis, dyspnoea, cough and increased liver enzymes.
One of the most serious adverse events that can occur prescribing metformin is lactic acidosis. Other side effects are primarily gastrointestinal, including abdominal pain, bloating, nausea, diarrhoea and anorexia.

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

-Cytological or histological confirmed carcinoma of the pancreas
-Measurable lesion according to RECIST criteria
-ECOG/ WHO performance 0-2
-Age > 18 years
-Life expectancy > 3 months
-Adequate renal function (creatinine < 150 µmol/L and/ or a creatinine clearance > 60 ml/ L)
-Adequate liver function (bilirubin < 1.5 times upper limit of normal, ALAT or ASAT < 5.0 times upper limit of normal in case of liver metastases and < 2.5 the upper limit of normal in absence of liver metastases).
-Adequate bone marrow function (WBC > 3.0 x 10 9/L, platelets > 100 x 10 9/L)
-Mentally, physically, and geographically able to undergo treatment and follow up

Exclusion criteria

-Clinical or radiological evidence of CNS metastases
-Pregnancy (positive serum pregnancy test) and lactation
-Serious concomitant systemic disorder that would compromise the safety of the patient, at the discretion of the investigator
-Patients who have any severe and/or uncontrolled medical conditions such as:
* unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction
* 6 months prior to randomization, serious uncontrolled cardiac arrhythmia,
* uncontrolled diabetes as defined by fasting serum glucose >2X ULN.
* active or uncontrolled severe infection.
* cirrhosis, chronic active hepatitis or chronic persistent hepatitis

* severely impaired lung function
-Previous treatment with erlotinib and/ or gemcitabine
-Patients with a known hypersensitivity to metformin
-Use of metformin in the previous 6 months

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-06-2010
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	erlotinib
Generic name:	tarceva
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	gemcitabine
Generic name:	gemzar
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	metformin
Generic name:	glucophage
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	30-12-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2009-017716-32-NL
CCMO	NL30851.018.10