Phase I study evaluating indomethacin in combination with platinum-based chemotherapy

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Phase I study to investigate safety of the combination indomethacin and two platinum-based chemotherapy regimens in patients with advanced cancers.

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

Summary

ID

NL-OMON45105

Source
ToetsingOnline

Brief title
PIFA-01

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Cancer, malignancy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Fatty acids, Indomethacin, Platinum, Resistance

Outcome measures

Primary outcome

Primary endpoints: Safety of the combination of platinum-based therapy and

indomethacin.

Secondary outcome

Secondary endpoints: Pharmacodynamics of the combination of platinum-based

chemotherapy and indomethacin. Efficacy. Tolerability.

Study description

Background summary

Mesenchymal stem cells (MSCs) are present in the circulation of cancer patients, and are recruited to the stroma of both the primary tumor and metastasis. Recent preclinical research has shown that in response to platinum-based chemotherapy, MSCs secrete two specific platinum-induced fatty acids (PIFAs) which induce resistance to a broad spectrum of chemotherapies. The secreted PIFAs are the fatty acid oxo-heptadecatetraenoic acid (KHT) and the omega-3 fatty acid hexadecatetraenoic acid (16:4). These PIFAs are produced via the COX-1 pathway. COX inhibitors, including indomethacin, but not selective COX-2 inhibitors, prevented the MSC induced resistance and enhance chemotherapy efficacy in preclinical studies.

Study objective

Phase I study to investigate safety of the combination indomethacin and two platinum-based chemotherapy regimens in patients with advanced cancers.

Study design

Phase I, non-randomized, dose-escalation study for the combination of platinum-based chemotherapy and indomethacin is comprised of two arms: arm I : patients with advanced carcinoma receiving cisplatin combined with gemcitabine or 5FU/capecitabine. (cisplatin dose range 60-80 mg/m2).

arm II : patients receiving CAPOX (oxaliplatine, capecitabine).
The dose of indomethacin will be escalated in each arm to a maximum of 225 mg per day, in a 3+3 design.

Intervention

All patients will receive their first chemotherapy cycle according standard of care without addition of indomethacin. If no toxicity as defined in table 3.1.1 is observed Indomethacin will be administered orally 8 days around the chemotherapy infusion from the second cycle and beyond, starting 2 days before until 5 days after. Dosage of indomethacin will be escalated between cohorts if no DLT criteria are met. Indomethacin starting dose in the first cohort will be three times 25 mg per day and escalated in a second cohort to three times 50mg per day, and a third cohort of 3 times 75 mg per day. All patients will use proton pump inhibition (PPI) from 1 week before start of the 2nd cycle and continue during the remainder of the study protocol to prevent gastric stress ulcers. Per treatment arm each cohort consists of 3 patients, which can be expanded to 6 patients if indicated according dose escalation rules.

Study burden and risks

Potential risks:
The potential risks follow from the known toxicity of cisplatin, oxaliplatin and indomethacin and a potential enhancement of these toxicities due to the combination of the two agents.
Both cisplatin, oxaliplatin and indomethacin are registered in The Netherlands and the toxicity profiles, contra-indications and interactions are extensively investigated and described.
Our department has broad experience with the administration of cisplatin and oxaliplatin. Indomethacin is a very well established drugs used for a broad range of indications in and outside the hospital.
Due to the combination of both agents the risk of nephrotoxicity, mainly with cisplatin, bone marrow depressions and gastro-intestinal side effects might be increased and this will be monitored very carefully as described in section 7.4.2.
It should be noted however that indomethacin is only administered 7 days of each cycle, were usually, eg in patients with rheumatic arthritis, indomethacin is taken for a prolonged period in row.

Potential benefits:
Given the results of our preclinical studies, as described in the introduction, we expect that the addition of indomethacin will enhance the chemotherapy efficacy and prevent the development of resistance of platinum-based chemotherapy, and will therefore lead to an enhanced progression free and overall survival.

Concluding, the preclinical data generated till now did provide evidence for a beneficial effect for the addition of indomethacin to cisplatin or oxaliplatin. The preclinical and clinical data available and safety assessments as part of this study provide confidence that this trial can be safely executed.

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

- Subjects with a histological proven malignancy receiving cisplatinum combined with gemcitabine or 5FU/capecitabin (dose range cisplatin 60-80 mg/m2) (Arm I) or CAPOX (oxaliplatin, capecitabine) (Arm II) in a 21 day cycle.
- Platinum*based chemotherapy naïve for at least 6 months.
- Age * 18 years.
- Subjects with at least one evaluable lesion.

- WHO Performance Status of 0 or 1.
- Female participants should be of non-child bearing potential either physiologic or by using adequate contraception, have a negative serum pregnancy test, and refrain from breast feeding.
- Written informed consent.

Exclusion criteria

- Known or suspected allergy or hypersensitivity to indomethacin or any agent given in association with this trial, in particular subjects who have a history of severe hypersensitivity reactions to anti-emetics (5-HT3 antagonists, metoclopramide or corticosteroids) and acetylsalicylic acid or other prostaglandin synthethase inhibitors.
- Symptomatic brain or meningeal tumors
- Subjects with seizure disorder requiring medication (such as steroids or anti-epileptics).
- Any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
- Uncontrolled high blood pressure, history of labile hypertension, or history of poor compliance with an antihypertensive regimen
- Unstable angina pectoris
- Symptomatic congestive heart failure NYHA class * 3 (see appendix 13.6)
- Myocardial infarction * 6 months prior to randomization
- Serious uncontrolled cardiac arrhythmia
- Active peptic ulcer disease, gastritis, inflammatory bowel disease.
- History of active gastro-intestinal bleeding
- History of cerebro-vascular disease
- Bleeding diathesis
- Chronic renal disease defined as GFR (MDRD) < 60 ml/min
- Absolute Neutrophil Count (ANC) < 1.5 x 109/L (< 1500/mm3)
- Platelets (PLT) < 100 x 109/L (* 100,000/mm3)
- Hemoglobin (Hgb) < 6.0 mmol/l (patients may be transfused to achieve adequate Hb)
- Partial thromboplastin time (PTT) > 1,5 x ULN
- Serum bilirubin > 1.5 ULN
- Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) > 3.0 x ULN (> 5 x ULN if liver metastases present)
- Patients who are unable or unwilling to comply with the protocol
- Chronic treatment with a corticosteroid agent (nebulized corticosteroids are allowed)
- Patients who received radiation therapy within 4 weeks of the start of the study
- Patients who received an experimental agent less than 4 weeks before start of the study.
- Patients who used Omega-3/omega-6 containing products, including fish oil products less than 2 weeks before start of the study.
- Chronic use of NSAID*s and/or acetylsalicylic acid and/or other prostaglandin synthethase inhibitors.
- Use of anticoagulant therapy

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):	24-10-2012
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cisplatin
Generic name:	Cisplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Eloxatin
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Indometacin
Generic name:	Indometacin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Losec
Generic name:	Omeprazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-08-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-08-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-12-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-03-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-01-2014

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-09-2017

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2012-001860-32-NL
ClinicalTrials.gov	NCT01719926
CCMO	NL40487.041.12