Phase Ib/II study of metformin in combination with carboplatin/paclitaxel chemotherapy in patients with advanced ovarian cancer

Published: 19-03-2014
Last updated: 20-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON40143

Source
ToetsingOnline

Brief title
OVMET

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
cancer of the ovaries, ovarian cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: carboplatin, metformin, ovarian cancer, paclitaxel

Outcome measures

Primary outcome

The primary end-point of the phase I study is the recommended phase II dose based on dose-limiting toxicities and maximum tolerated dose of metformin in combination with carboplatin/paclitaxel.

The primary end-point of the phase II study is objective response rate in patients with measureable disease and CA-125 response as defined by the Gynaecologic Cancer Intergroup (GCIG) for non-measurable disease.

Secondary outcome

The secondary end-points are:

• All adverse events and laboratory events coded and graded by the CTCAEv4 criteria

• Percentage of patients in which complete debulking is achieved (residual disease <1cm)

• Percentage of patients with a complete pathological response

• Objective tumour response by RECIST version 1.1 in patients with measurable disease

• Objective tumour response by CA-125 criteria in patients without measurable disease

• Progression free survival and overall survival distributions

• Exploratory analysis of paired pre-and post treatment immunohistochemical

tumour tissue biomarker expression as described in translational research

section

• Exploratory analysis of paired pre-and-post treatment serum biomarker levels

as described in the translational research section

• Exploratory analysis of metformin concentrations in tumour cells as described

in the translational research section

Study description

Background summary

Molecularly targeted agents which inhibit the mTOR pathway and/or circumvent p53 in the induction of apoptosis are exciting potential targets in ovarian cancer. Metformin is a biguanide, widely used in the treatment of type 2 diabetes mellitus, that has shown anti-cancer activity in preclinical models of ovarian cancer. The main mechanism of metformin*s effect is mTOR pathway inhibition and, in addition, it has been shown to circumvent p53-induced apoptosis making it an exciting, potentially effective drug in ovarian cancer.

Study objective

The primary objective of the phase I part of the study is to determine the recommended phase II dose of metformin in combination with carboplatin/paclitaxel chemotherapy in patients with advanced ovarian cancer. The secondary objectives the phase I study are to document the safety profile of metformin in combination with carboplatin/paclitaxel chemotherapy and to document the influence of metformin on the pharmacokinetics of carboplatin/paclitaxel chemotherapy.

The primary objective of the second phase of this study is to determine the activity of adding metformin to carboplatin/paclitaxel neoadjuvant chemotherapy in patients with advanced stage ovarian cancer. The secondary objectives are to determine safety and tolerability, likelihood of complete tumour debulking, likelihood of complete pathological response and the patient outcome and to explore tumour and serum biomarkers and intratumoral metformin concentrations.

Study design

A phase Ib, single-centre, dose-escalation trial of metformin given in combination with carboplatin and paclitaxel chemotherapy in patients with advanced ovarian cancer, with a traditional escalation rule with fixed dose levels (*3 + 3* rule). The recommended phase II dose will be defined as the maximum predefined dose level at which 0 of 3 or <= 1 of 6 subjects experience a drug-related DLT during cycle 1 and 2 of treatment. An estimated 10-20 patients will be required for this part of the study.

An open-label, single-centre, randomised, controlled phase II study in advanced ovarian cancer patients eligible for neoadjuvant chemotherapy followed by surgical debulking and adjuvant chemotherapy. The control arm will receive three 21-day cycles of paclitaxel/carboplatin neoadjuvant chemotherapy followed by cytoreductive surgery and thereafter three adjuvant cycles. The treatment arm will additionally receive continuous dosing of metformin, at the recommended phase II dose as determined in the phase I part of this trial, during chemotherapy treatment. 44 patients will be included initially, if sufficient responses are seen an additional 60 patients will be entered

Intervention

Phase I: Carboplatin/paclitaxel chemotherapy in combination with escalating doses of metformin

Phase II: Carboplatin/paclitaxel chemotherapy with or without metformin at recommended phase II dose

Study burden and risks

Metformin is a widely prescribed, safe oral anti-diabetic drug with a known, relatively mild side-effect profile. There is preclinical evidence for an anti-cancer effect. In combination with standard carboplatin/paclitaxel chemotherapy it may enhance response rates and improve outcome. Burden of participation will be kept to a minimum with the majority of the study visits coinciding with routine treatment visits. Besides blood sampling, no additional diagnostic procedures are required.

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 advanced stage (FIGO III-IV), histologically confirmed and documented epithelial ovarian carcinoma
•Patients eligible for neoadjuvant carboplatin/paclitaxel chemotherapy prior to surgical debulking (phase 1 or 2) OR patients with relapsed or progressive ovarian cancer after initial treatment eligible for palliative carboplatin/paclitaxel chemotherapy (phase 1 only)
•Measurable tumour according to RECISTv1.1 or GCIG CA125 criteria (phase 2 only)
•Eastern Cooperative Oncology Group-performance status (ECOG-PS) of 0-2
•Age >= 18 years
•Adequate blood count, hepatic and renal function
•Written informed consent

Exclusion criteria

•Prior chemotherapy, immunotherapy, targeted agents or radiotherapy to abdomen or pelvis (phase 2 only)
•Current or recent (within 30 days of first study dosing) treatment with another investigational drug or participation in another investigational study.
•Metformin within 4 weeks prior to enrolment.
•Other malignancy within the last 5 years, except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin

cancer (phase 2 only)
•Symptomatic CNS metastasis
•Pre-existing peripheral neuropathy >= CTC grade 2.
•Pregnant or lactating females. Serum pregnancy test to be assessed within 7 days prior to study treatment start, or within 14 days with a confirmatory urine pregnancy test within 7 days prior to study treatment start.
•Women of childbearing potential (defined as <2 years after last menstruation and not surgically sterile) not using effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly) during the study and for 6 months after the last study medication.
•Known hypersensitivity to any of the study drugs or excipients.
•Serious active infection requiring i.v. antibiotics at enrolment.
•Unstable medical conditions.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-10-2015
Enrollment:	124
Type:	Actual

Medical products/devices used

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

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Metformin
Generic name:	Metformin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	paclitaxel
Generic name:	paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-03-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-12-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-005050-35-NL
CCMO	NL47539.042.14