Phase 0 proof of concept study: a clinical pharmacokinetic microdosing trial with gemcitabine

Published: 23-01-2017
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To ascertain whether the pharmacokinetics of gemcitabine in a therapeutic dose can be predicted from the pharmacokinetics of a microdose.

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

Summary

ID

NL-OMON45398

Source
ToetsingOnline

Brief title
N16GEM: Gemcitabine microdosing trial

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
metastatic bladder cancer and malignant mesothelioma, Metastatic non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Startgeld Antoni van Leeuwenhoek

ziekenhuis

Intervention

Keyword: Gemcitabine, Microdosing, pharmacokinetics

Outcome measures

Primary outcome

To study the pharmacokinetics after administration of a microdose and the

pharmacokinetics after administration of a therapeutic dose.

Secondary outcome

To analyse patient plasma with liquid chromatography-mass spectrometry

(LC-MS/MS)

Study description

Background summary

Phase 0 microdose studies can be conducted prior to phase 1 in drug development to study the pharmacokinetics a certain drug. These pharmacokinetics are thought to predict the pharmacokinetics after administration of a therapeutic dose. Curretly, 11 phase 0 microdose trials have been published. During such a trial, it is unknown whether the pharmacokinetics are indeed scalable to the pharmacokinetics of a therapeutic dose. None of these studies have been conducted with chemotherapeutics.

Gemcitabine is a drug that can be prescribed for several types of cancer. It is a chemotherapeutic drug that belongs to the group of antimetabolites. Gemcitabine is metabolised intracellularly to diphosphate- and triphosphatenucleosides (dFdCDP and dFdCTP). Gemcitabine triphosphate inhibits DNA-synthesis by inhibition of ribonucleotide reductase: this enzyme catalyses the production of deoxynucleoside triphospates (dCTP). Gemcitabine triphosphates compete with dCTP for DNA incorporation. This incorporation inhibits DNA sythesis and eventually induces apoptosis.

Study objective

To ascertain whether the pharmacokinetics of gemcitabine in a therapeutic dose

can be predicted from the pharmacokinetics of a microdose.

Study design

This is a phase 0 prospective, single-center, open-label microdosing study. Eligible patients consecutively receive a microdose (100 *g) and a therapeutic dose (1000 * 1250 mg/m2) of gemcitabine with a 1-day interval as shown in Figure 1. Only patients who are qualified for gemcitabine therapy according to standard of care can enroll in this study. Blood will be drawn for pharmacokinetic research at 11 time points a day

Intervention

Administration of a microdose

Study burden and risks

A microdose is considered harmless and nontoxic as the administered dose is just a small portion of the therapeutic dose. Therefore, we qualify the risk of this study as *low*. This is motivated by the following:
1) The study drug is registered for clinical use.
2) Multiple studies in these patient categories with the study drug have been performed before.
3) A microdose is considered harmless and non-toxic.

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

1. Age > 18 years.
2. Indication for treatment with gemcitabine.
3. Histologically or cytologically confirmed diagnosis of:
a. Locally advanced or metastatic non-small cell lung cancer.
b. Locally advanced or metastatic bladder cancer.
c. Malignant mesothelioma
4. Able and willing to give written informed consent.
5. WHO performance status of 0 or 1.
6. Able and willing to undergo blood sampling for PK analysis.
7. All toxicities related to prior treatment should have resolved to CTCAE grade 1 or less.
8. Willing and able to comply with study restrictions and to remain at the study center for the required duration.
9. Adequate organ system function.

Exclusion criteria

1. Known hypersensitivity to gemcitabine.
2. Prior treatment with gemcitabine within 30 days of the first dose.
3. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or that may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for the study.
4. Active, uncontrolled systemic infection considered opportunistic, life threatening, or clinically significant at the time of treatment.
5. Known positive test result for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (HC Ab) or has a known positive test result for human immunodeficiency virus (HIV) or a history of HIV disease.
6. Serious medical or psychiatric condition that, in the opinion of the Investigator, should preclude the patient from participating in the study.

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):	11-05-2017
Enrollment:	10
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	23-01-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	09-03-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	16-08-2018
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	EUCTR2016-004595-22-NL
CCMO	NL59891.031.17