Phase I/II study of oxaliplatin combined with melphalan in isolated hepatic perfusion for the treatment of liver metastases.

Published: 05-10-2006
Last updated: 09-05-2024

Firstly, determination of the maximum tolerated dose (MTD) , dose limiting toxicity (DLT) and farmacokinetics in IHP with sequential administration of oxaliplatin and melphalan.Secondly, evaluation of toxicity, tumor response and survival after IHP...

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

Summary

ID

NL-OMON30309

Source
ToetsingOnline

Brief title
Oxaliplatin combined with melphalan in IHP.

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
liver metastases, secondary liver tumours

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

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

Intervention

Keyword: Isolated Hepatic Perfusion, Liver metastases, Melphalan, Oxaliplatin

Outcome measures

Primary outcome

- Determination of the maximum tolerated dose (MTD) , dose limiting toxicity (DLT) and farmacokinetics in IHP with sequential administration of oxaliplatin and melphalan

-Determination of phase II doses of oxaliplatin and melphalan.

Secondary outcome

-Evaluation of toxicity (CTCAE version 3.0), tumor response and survival after IHP with sequential administration of oxaliplatin and melphalan at the MTD previously determined.

Study description

Background summary

In the Netherlands 8400 patients are diagnosed with colorectal cancer each year. Approximately 50% of these patients develop liver metastases. If these metastases are confined to the liver, complete surgical resection is possible in 25% of patients, resulting in a median survival of 32-46 months. In 75% of the patients with metastases confined to the liver, resection is impossible due to size or localization of metastases. For these patients systemic chemotherapy remains the only treatment option. One of the major drawbacks of systemic treatmentis that the maximum tolerable dose has been achieved before the minimal active dose has been adminstered. To improve results in patients with irresectable liver metastases, isolated hepatic perfusion (IHP) has been developed. In the past years melphalan, a relatively old drug, has been the only drug applied in IHP. In systemic chemotherapy, on the other hand, several new agents, including oxaliplatin have been introduced succesfully. Oxaliplatin is rapidly absorbed and transformed to its active form. In studies where

oxaliplatin is administered systemically hepatotoxicity is raley mentioned. In vitro studies have shown a schedule dependent synergistic interaction between melphalan and oxaliplatin.

Study objective

Firstly, determination of the maximum tolerated dose (MTD) , dose limiting toxicity (DLT) and farmacokinetics in IHP with sequential administration of oxaliplatin and melphalan.
Secondly, evaluation of toxicity, tumor response and survival after IHP with sequential administration of oxaliplatin and melphalan at the MTD previously determined.

Study design

This is a singlecenter, combined phase I/I study. Patients who are eligable for this study will be treated once with a escalating dose of oxaliplatin combined with melpalan untill the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) have been achieved. After which another 40 patients will be treated with the MTD. Treatment will be evaluated at a 3 month interval (6 month interval after 1 year) thruogh CT-scans untill progression of liver disease has occured.

Intervention

Single isolated hepatic perfusion with an escalating dose of oxaliplatin (initial dose 50mg, with 50mg incease each escalation) for 30 minutes, followed by 30 minutes perfusion with 100mg melphalan.

Study burden and risks

Patients will undergo a full medical examination. Laboratory testing, CT scans of thorax and abdomen will be performed as to establish extent of disease and operability.
The risks of IHP are either associated to the surgical procedure (dissection, bleeding, infection, etc), similar to the standard procedure, or are the risks (both liver toxicity and systemic toxicity) associated to the administration of oxaliplatin and melphalan (see also page 22-23 of the study protocol).
After perfusion patients will undergo laboratory testing en imaging (CT scan) every three months untill liver progression occurs.

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

- Livermetastases of histologically confirmed colorectal adenocarcinoma and for the phase I also livermetastases from solid tumors other than colorectal carcinoma.
- Resection of primary tumor > 1 month prior to IHP
- Irresectabel metastes confined to the liver.
- Measurable metastases on CT-scan
- Informed consent
- Life expectancy > 4 months
- Leukocytes >= 3.0 X 109/L
- Thrombocytes >= 100 X 109/L
- Clearance >= 40 ml/min
- Bilirubin <17 µmol/L
- APTT < 32.5 sec
- PT < 13.7 sec

Exclusion criteria

- Biological age <18 years >65 years
- WHO performance status larger or equal to 2
- < 40% viabel liver tissue
- Vascular anatomy which inhibits the procedure (ie aberrant right or left hepatic artery, severe atherosclerosis, vascular dissections)
- Simultaneous severe medical problem (ie severe heart/vascular disease, diabetes with nefropathy, active infection and other liver disease)
- Mental retardation
- Pregnancy or inadequate anticonception

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2007
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Alkeran
Generic name:	Melphalan
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Eloxatin
Generic name:	Oxaliplatin

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-10-2006
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2006-005088-25-NL
CCMO	NL14502.058.06