Free circulating tumour DNA in patients with peritoneal metastases of colorectal origin and HIPEC therapy; LIBEC trial - a feasibility study

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To evaluate the detection ctDNA in patients with PC of colorectal origin undergoing cytoreductive surgery and HIPEC at time of diagnosis in a feasibility trial This study is considered feasible:1. If in at least 70% of the patients ctDNA status...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON43017

Source
ToetsingOnline

Brief title
LIBEC trial

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Peritoneal metastases

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Colorectal, ctDNA, HIPEC, Liquid Biopsy

Outcome measures

Primary outcome

Plasma levels of ctDNA preoperatively and postoperatively

-qualitative: is mutated ctDNA detectable yes or no?

-quantitative: the ratio between the number of mutated ctDNA reads to the total

number of ctDNA reads

Secondary outcome

Patient characteristics

Tumour characteristics

Descriptives only.

Study description

Background summary

Peritoneal carcinomatosis (PC) of colorectal origin occurs in 13 per cent of the patients at time of diagnosis and 25% of the patients develop PC at recurrence. Prognosis for PC without aggressive therapy is poor. Without treatment, median survival is approximately 3 months. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has been reported to have significant benefit on survival of peritoneally metastasized gastro-intestinal and gynaecological carcinomas. Median survival of patients

with PC of colorectal origin has improved with 21-30 months and 30 to 50% 5-year survival7.

Major difficulty and intense focus of research for CRS and HIPEC is patient selection. Curative CRS and HIPEC is only achieved in patients with limited disease, defined by either the PCI (Peritoneal Carcinomatosis Index) or the recently introduced PSDSS (Peritoneal Surface Disease Severity Score). A disadvantage of both scoring systems is that intraoperative assessment of peritoneal disease is required. Patients with disease that is too extensive do not undergo CRS and HIPEC resulting in 23.4% unnecessary explorative procedures. Preoperative imaging does not accurately deflect the amount of peritoneal metastases. CT alone has poor sensitivity of 11% for nodules smaller than 0,5 centimetres. Also radiological PCI scores significantly underestimate intraoperative PCI.

Second major field of interest is to improve detection of recurrent disease after CRS and HIPEC with curative intent. A recent study presented 46% recurrence rate after a median disease-free survival of 11.4 months. Recurrences were locoregional (43%), distant metastases (26%) or both (31%). Optimal treatment of recurrent locoregional disease is repeat CRS and HIPEC, extending median survival with 43 months.
Postoperative follow-up of patients after HIPEC is routinely performed every three months with physical examination, laboratory carcinoembryonic antigen (CEA) tumour marker levels and biannual CT-scan of abdomen, liver and lungs. CEA, however, has poor sensitivity (30-40%) or specificity (87%) for detection of recurrence. Normal CEA values may be found in almost 50% of cancers before surgical resection and often do not rise during recurrences1. CEA elevation also has a slow lead time predating the clinically identifiable recurrence by approximately 5 months.
Imaging by (PET)/CT or MRI does not accurately detect PC unless advanced stage of metastases are present. Follow-up with CEA and CT-scan, as is standard, can often result in late diagnosis of recurrent disease, therefore limiting treatment options due to either extensive locoregional recurrence or distant metastases for many patients.

In the past decade studies have been performed evaluating the diagnostic and prognostic value of free circulating tumour DNA (ctDNA). It is proposed that ctDNA is released into the circulation and is present in plasma and serum. The precise mechanism of the release of DNA into the bloodstream remains to be proven. Accordingly, it is possible to detect ctDNA, such as genetic or epigenetic alterations identified in the primary tumour DNA, in the serum of patients with various cancers. Several tumour-specific circulating DNA markers have been identified to have diagnostic and prognostic value in primary colorectal cancer. Also ctDNA have been proven valuable for follow-up of patients after resection of primary colorectal cancer.

In patients with colorectal cancer, ctDNA was detected in 73% of patients and up to 95% in patients with metastatic disease. In 206 patients with metastatic colorectal cancer sensitivity of clinically relevant KRAS mutations was 87.2% with specificity of 99.2%. In healthy patients or in patients with colitis the level of ctDNA was undetectable. Also in other adenocarcinomas it has been shown feasible to detect ctDNA; in patients with pancreatic cancer. Detection of ctDNA after resection predicts recurrence and poor outcome, with recurrence by ctDNA detected 6.5 months earlier than with CT imaging.

Previous studies have focussed to other types of circulating tumour material such as circulating tumour cells, or DNA fragments. A major advantage of ctDNA is its specificity for the mutations which are present in the individual patient, since specific mutations are looked for in the plasma that have previously been detected in the solid surgical resection specimens. Therefore it is less prone to have high false positivity as is the case in DNA fragment detection. Also ctDNA is technically more feasible for detection in blood compared to circulating tumour cells.

The value of ctDNA could be a valuable asset as prognostic and diagnostic marker in patients with peritoneal metastases.
Aim is to investigate the feasibility of ctDNA after cytoreductive surgery and HIPEC.

Study objective

To evaluate the detection ctDNA in patients with PC of colorectal origin undergoing cytoreductive surgery and HIPEC at time of diagnosis in a feasibility trial

This study is considered feasible:
1. If in at least 70% of the patients ctDNA status correlates with mutational status of the tissue specimen preoperatively (qualitative)
2. If in at least 50% of the patients with detectable mutated ctDNA show decreased levels of ctDNA after treatment (quantitative)

If this study has proven feasible, a prospective multicenter cohort study will be proposed.

Study design

Feasibility study. VU University Medical Centre.
Two blood samples (2*9ml Streck tubes per moment) are taken during a period of several weeks

Preoperative
- Venous blood sample (18mL) (after anaesthesia, taken from central venous line before first surgical incision)

Early postoperative
- Venous blood sample (18mL) 2-4 weeks postoperative

Study burden and risks

Potential issue of concern is the very small chance of a complication following venapunction. These include:
- Excessive bleeding
- Fainting of feeling light-headed / venapunction related anxiety
- Hematoma or blood accumulating under the skin
- Pain

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

- Orally and written informed consent
- Age 18 years and older
- Elective cytoreductive surgery followed by HIPEC
- Peritoneal metastases only
- Regular preoperative work-up

Exclusion criteria

- Patients who are legally or mentally incapable or unable to give informed consent
- Patients younger than 18 years
- Presence of liver metastases on CT-scan
- Presence of pulmonary metastases on CT-scan
- Anxiety for vena puncture

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-08-2016
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	17-08-2016
Application type:	First submission
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

ID: 22788
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL57226.029.16
OMON	NL-OMON22788

Study results

Date completed:	15-05-2018
Actual enrolment:	44