Feasibility study of biomarker development for response prediction by large scale DNA mutational analysis of metastatic lesions.

Published: 10-05-2011
Last updated: 27-04-2024

Primary objective:To determine the feasibility of developing predictive biomarkers by large scale DNA-sequencing for the response to irinotecan monotherapy as standard of care treatment for metastatic colorectal cancer or other solid tumors....

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

Summary

ID

NL-OMON39548

Source
ToetsingOnline

Brief title
CPCT - 01 trial

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
metastatic cancer, metastatic solid tumors

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: Feasibility study, Irinotecan, Metastatic colorectal cancer or other solid tumors for which irinotecan is standard of care treatment, Predictive biomarker

Outcome measures

Primary outcome

Exploration of the correlation between percentage change in volumetric measurement of the index lesion and the mutational profile after the first two cycles of chemotherapy.

Secondary outcome

Secondary endpoints:

- Exploration of the correlation between radiological response according to RECIST-criteria and the mutational profile after each two cycles of chemotherapy.

- Exploration of the correlation between progression free survival and overall survival with the mutational profile.

- Explore the correlation between patient*s germline DNA background variation and mutational profile of the metastasis.

- Differences in mutational profile of the metastasis prior to and after exposure to treatment.

- Determine reliable and valid strategies for statistical analysis for biomarker discovery.

Tertiary endpoints:

- Correlate response to the pharmacokinetics of SN-38.

- Determine carboxylesterase (hCE1 and hCE2) activity in metastatic tumor material (pre- and post-treatment) and correlate intra-tumoral carboxylesterase activity to systemic SN-38 pharmacokinetics and to irinotecan response.

- Number and nature of all (serious) adverse events of study related procedures.

Study description

Background summary

Current chemotherapeutic regimens demonstrate response rates that could be improved.
Hence, patients are exposed to (potential) harmful chemotherapeutic agents without knowing whether or not they will respond to and benefit from treatment. One of the focuses of molecular genetic research is to find biomarkers predicting response to treatment and next-generation DNA sequencing is a highly promising technology for this purpose. Genetic discrepancies can be seen between metastases and the primary tumor. Therefore it is necessary to study the mutational profile of safely and easily accessible metastatic lesions.

With this feasibility study we specifically aim to explore whether it is possible to develop a predictive biomarker for chemotherapy response based on next-generation DNA sequencing data, under ideal circumstances. For this, we focus on a setting with 1. Relatively low heterogeneity in molecular pathways leading to chemotherapy response (i.e. a monotherapeutic regimen: standard of care treatment with irinotecan for metastatic colorectal cancer or other solid tumors); 2. A primary endpoint most likely to be associated with the measured genetic profile (i.e. short-term treatment response of the metastasis used for DNA sequencing); and 3. Maximal contrast (i.e. comparing the best with the worst responders).

Colorectal cancer is the third most common adult malignancy worldwide, Approximately 20% of patients with colorectal cancer present with distant metastasis (stage IV) at time of diagnosis, with a 5-year survival rate of approximately 10%. Significant progress has been made in the treatment of metastatic colorectal cancer, resulting in prolonged median survival from five months to approximately two years. Irinotecan monotherapy has been widely accepted as standard of care second line treatment with response rates of only

10-17%. No predictive biomarkers for irinotecan response have been found yet, although response may correlate to plasma levels of the active metabolite (SN-38) or carboxylesterase activity within the tumor.

For the proposed study we have chosen to select patients with metastases from colorectal cancer, who have failed first-line palliative treatment and are irinotecan naïve. This is explicitly not a drug study: patients will receive standard of care second-line treatment with irinotecan monotherapy. Prior to intervention with irinotecan patients will be subjected to a histological biopsy of a metastatic lesion for DNA sequencing and analysis of carboxylesterase. In case of definitive discontinuation of irinotecan (at any time point for any reason) patients will again be subjected to a histological biopsy. Additional analyses consist of blood samples for pharmacogenetic research, pharmacokinetic analysis of circulating SN-38 (the active metabolite) during first administration of irinotecan.

Study objective

Primary objective:
To determine the feasibility of developing predictive biomarkers by large scale DNA-sequencing for the response to irinotecan monotherapy as standard of care treatment for metastatic colorectal cancer or other solid tumors.

Secondary objectives:
- To explore the correlation between survival and mutational profile of the index lesion.
- To relate pharmacogenetics to the primary objective of the study.
- To determine changes in mutational profile of metastasis under the influence of chemotherapy.
- To aid the development of strategies for statistical analysis by generation of valuable human data.

Tertiary objectives:
- To correlate plasma pharmacokinetics of the active irinotecan metabolite (SN-38) to the efficacy of irinotecan treatment.
- To determine carboxylesterase activity for irinotecan response apart from the mutational profile and pharmacokinetics.
- To determine the safety of study related procedures.

Study design

Observational prospective multicenter biomarker discovery cohort study.

Study burden and risks

Burden in time for the individual patient:

- baseline screening: approximately 3 hours
- biopsy: 2 x 3 hours (biopsy itself approximately 15-30 minutes, afterwards observation for at least 2 hours)
- pharmacokinetics: 24 hours (with an optional hospital admission overnight)

Burden of invasive procedures:
- 2 biopsies of a metastasis
- 13 (or 21; for Rotterdam cohort of patients) x 5 ml additional blood draws: 1 x 5 ml + 1 x 10 ml for pharmacogenetic analysis, 11 x 5 ml for pharmacokinetic analysis (cycle 1: day 1 10 blood draws and day 2 1 blood draw with an optional hospital admission overnight). The 11 additional blood samples will be taken from a placed intravenous access

Risks: there is a small chance on complicatons (specified in Appendix C):
- biopsy: pain, bleeding, infection, allergic reaction
- blood draws: pain, hematoma, infection

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

Metastatic colorectal carcinoma or other solid tumors
Failed at least one line of palliative chemotherapy
Irinotecan naïve
Eligible, as per local protocol, for palliative treatment with standard of care irinotecan
Measurable metastatic lesion(s) according to RECIST 1.1. criteria
Safe biopsy of a radiological measurable lesion possible
Adults age 18 years or up
Written informed consent

Exclusion criteria

Patients with other malignancies than metastatic colorectal cancer or other solid tumors
Patients eligible for first-line treatment
Patients who were already subjected to treatment with irinotecan
Patients with disease not measurable according to RECIST 1.1. criteria
Safe biopsy of radiological measurable lesion not possible
Patients younger than 18 years old
Patients not willing to sign informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-11-2011

Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	10-05-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-09-2014
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
Other	Het onderzoek gaat ook geregistreerd worden op clinicaltrials.gov
CCMO	NL35198.041.11