Chemo-immunotherapy before and after surgery for peritoneal metastases of large bowel cancer

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21182

Source
NTR

Brief title
CAIRO6

Health condition

Colorectal cancer with isolated peritoneal metastases

Sponsors and support

Primary sponsor: Catharina Hospital
Michelangelolaan 2
5623 EJ, Eindhoven
The Netherlands
Source(s) of monetary or material Support: 1. Dutch Cancer Society
2. Roche Netherlands B.V.

Intervention

Outcome measures

Primary outcome

Outcomes of the phase II study are to explore:

• the feasibility of accrual, based on the total accrual rate, the accrual rate in each study centre, and screening failures (time point: not applicable);

• the feasibility of perioperative systemic therapy, based on the number of patients that (1) start/complete neoadjuvant systemic therapy with/without dose reductions, (2) are scheduled for CRS-HIPEC, (3) undergo complete CRS-HIPEC, and (4) start/complete adjuvant systemic therapy with/without dose reductions (time point: six to nine months after randomisation);

• the safety of perioperative systemic therapy, based on the number of patients with (1) systemic therapy related toxicity, defined as grade ≥2 according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, up to one month after the last administration of systemic therapy, and (2) postoperative morbidity, defined as grade ≥2 according to Clavien-Dindo, up to three months after CRS-HIPEC (time point: six to nine months after randomisation);

• the tolerance of perioperative systemic therapy, based on health-related quality of life extracted from EQ-5D-5L, QLQ-C30, and QLQ-CR29 during study treatment (time point: six to nine months after randomisation);

• the radiological and histological response of colorectal PM to neoadjuvant systemic therapy, based on central review of thoracoabdominal CT and resected specimens during CRS-HIPEC, respectively (time point: three to four months after randomisation).

The primary outcome is 3-year overall survival, defined as the number of patients who are alive three years after randomisation (time point: three years after randomisation).

Secondary outcome

Secondary outcomes of the phase III study in both arms are:

• progression-free survival, defined as the time between randomisation and disease progression before CRS-HIPEC, CRS-HIPEC in case of unresectable disease, radiological proof of recurrence, or death (time point: three years after randomisation);

• disease-free survival, defined as the time between CRS-HIPEC and radiological proof of recurrence or death (time point: three years after randomisation);
• health-related quality of life, extracted from questionnaires (EQ-5D-5L, QLQ-C30, QLQ-CR29) before study treatment, after neoadjuvant systemic therapy (experimental arm), every three months after CRS-HIPEC until one year postoperatively, and every six months thereafter until five years after randomisation (time point: three years after randomisation);

• costs, extracted from questionnaires (iMTA productivity cost questionnaire, iMTA medical

consumption questionnaire) before study treatment, after neoadjuvant systemic therapy (experimental arm), every three months after CRS-HIPEC until one year postoperatively, and every six months thereafter until five years after randomisation (time point: three years after randomisation);

• surgical characteristics, e.g. PCI, intraoperative complications, operating time, resections, completeness of cytoreduction, hospital stay (time point: three to four months after randomisation);

• the number of patients with major postoperative morbidity, defined as grade ≥3 according to Clavien-Dindo, up to three months after CRS-HIPEC (time point: six to nine months after randomisation).

Secondary outcomes in the experimental arm are:

• The number of patients with major systemic therapy related toxicity, defined as grade ≥3 according to the CTCAE, up to one month after the last administration of systemic therapy;

• The number of patients with an objective radiological and histological response of colorectal PM to neoadjuvant systemic therapy, determined by central review of thoracoabdominal CT and resected specimens during CRS-HIPEC, respectively. Classifications are determined after exploration of the radiological and histological response in the phase II study.

Study description

Background summary

Rationale: CRS-HIPEC is a curative intent treatment for patients with isolated resectable colorectal PM. Upfront CRS-HIPEC alone is the standard treatment in the Netherlands. The addition of neoadjuvant and adjuvant systemic therapy (together: perioperative systemic therapy) to CRS-HIPEC could have benefits and drawbacks. Potential benefits are eradication of systemic micrometastases, preoperative intraperitoneal tumour downstaging, elimination of post-surgical residual cancer cells, and improved patient selection for CRS-HIPEC. Potential drawbacks are preoperative disease progression and secondary unresectability, systemic therapy related toxicity, increased postoperative morbidity, decreased quality of life, and higher costs. Currently, there is a complete lack of randomised studies that prospectively compare the oncological efficacy of perioperative systemic therapy and CRS-HIPEC with upfront CRS-HIPEC alone. Notwithstanding this lack of evidence, perioperative systemic therapy is widely administered to patients with isolated resectable colorectal PM. However, administration and timing of perioperative systemic therapy vary substantially between countries, hospitals, and guidelines. More importantly, it remains unknown whether perioperative systemic therapy has an intention-to-treat benefit in this setting. Therefore, this

study randomises patients with isolated resectable colorectal PM to receive either perioperative systemic therapy (experimental arm) or upfront CRS-HIPEC alone (control arm).

Study design: a multicentre, open-label, parallel-group, phase II-III, superiority study that randomises eligible patients in a 1:1 ratio.

Objectives: objectives of the phase II study (80 patients) are to explore the feasibility of accrual, the feasibility, safety, and tolerance of perioperative systemic therapy, and the radiological and histological response of colorectal PM to neoadjuvant systemic therapy. The primary objective of the phase III study (an additional 278 patients) is to compare survival outcomes between both arms. Secondary objectives are to compare surgical characteristics, major postoperative morbidity, health-related quality of life, and costs between both arms. Other objectives are to assess major systemic therapy related toxicity and the objective radiological and histological response of colorectal PM to neoadjuvant systemic therapy.

Study population: adults who have a good performance status, histological or cytological proof of PM of a colorectal adenocarcinoma, resectable disease, no systemic colorectal metastases within three months prior to enrolment, no systemic therapy for colorectal cancer within six months prior to enrolment, no previous CRS-HIPEC, no contraindications for the planned systemic treatment or CRS-HIPEC, and no relevant concurrent malignancies .

Intervention: at the discretion of the treating medical oncologist, perioperative systemic therapy consists of either four 3-weekly neoadjuvant and adjuvant cycles of CAPOX, six 2-weekly neoadjuvant and adjuvant cycles of FOLFOX, or six 2-weekly neoadjuvant cycles of FOLFIRI followed by either four 3-weekly (capecitabine) or six 2-weekly (5-fluorouracil/leucovorin) adjuvant cycles of fluoropyrimidine monotherapy. Bevacizumab is added to the first three (CAPOX) or four (FOLFOX/FOLFIRI) neoadjuvant cycles.

Outcomes: outcomes of the phase II study are to explore the feasibility of accrual, the feasibility, safety, and tolerance of perioperative systemic therapy, and the radiological/histological response of colorectal PM to neoadjuvant systemic therapy. The primary endpoint of the phase III study is 3-year overall survival, which is hypothesised to be 50% in the control arm and 65% in the experimental arm, thereby requiring 358 patients (179 in each arm). Secondary endpoints are surgical characteristics, grade ≥3 postoperative morbidity, progression-free survival, disease-free survival , health-related quality of life, costs, major systemic therapy related toxicity, and objective radiological and histological response rates of colorectal PM to neoadjuvant systemic therapy.

Study objective

Patient with isolated resectable colorectal peritoneal metastases (PM) have a 3-year overall survival of 50% after upfront cytoreductive surgery with HIPEC (CRS-HIPEC) alone, and a 3-year overall survival of 65% after perioperative systemic therapy and CRS-HIPEC.

Study design

See primary and secondary outcomes

Intervention

At the discretion of the treating medical oncologist, perioperative systemic therapy consists of either:

• Four three-weekly neoadjuvant and adjuvant cycles of CAPOX (130 mg/m2body-surface area [BSA] of oxaliplatin, intravenously [IV] on day 1; 1000 mg/m2BSA of capecitabine, orally twice daily on days 1-14), with bevacizumab (7.5 mg/kg body weight, IV on day 1) added to the first three neoadjuvant cycles, or;

• Six two-weekly neoadjuvant and adjuvant cycles of FOLFOX (85 mg/m2BSA of oxaliplatin, IV on day 1; 400 mg/m2BSA of leucovorin, IV on day 1; 400/2400 mg/m2BSA of bolus/continuous 5-fluorouracil, IV on day 1-2), with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles, or;

• Six two-weekly neoadjuvant cycles of FOLFIRI (180 mg/m2BSA of irinotecan, IV on day 1; 400 mg/m2BSA of leucovorin, IV on day 1; 400/2400 mg/m2BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) and either four three-weekly (1000 mg/m2BSA of capecitabine, orally twice daily on days 1-14) or six two-weekly (400 mg/m2BSA of leucovorin, IV on day 1; 400/2400 mg/m2BSA of bolus/continuous 5-fluorouracil, IV on day 1-2) adjuvant cycles of fluoropyrimidine monotherapy, with bevacizumab (5 mg/kg body weight, IV on day 1) added to the first four neoadjuvant cycles.

Neoadjuvant systemic therapy should start within four weeks after randomisation. Adjuvant systemic therapy should start within twelve weeks after CRS-HIPEC. In case of unacceptable toxicity or contraindications to oxaliplatin or irinotecan in the neoadjuvant setting, CAPOX or FOLFOX may be switched to FOLFIRI and vice versa. In case of unacceptable toxicity or contraindications to oxaliplatin in the adjuvant setting, CAPOX of FOLFOX may be switched to fluoropyrimidine monotherapy. Dose reduction, co-interventions, and escape medication are not specified a priori, but left to the discretion of the treating medical oncologist. Perioperative systemic therapy can be prematurely discontinued due to radiological or clinical disease progression, unacceptable toxicity, physicians decision, or at patients request.

Contacts

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Eligibility criteria

Inclusion criteria

Eligible patients are adults who have:

• a World Health Organisation (WHO) performance status of ≤1;

• histological or cytological proof of PM of a non-appendiceal colorectal adenocarcinoma with ≤50% of the tumour cells being signet ring cells;

• resectable disease determined by abdominal computed tomography (CT) and a diagnostic laparoscopy/laparotomy;

• no evidence of systemic colorectal metastases within three months prior to enrolment;

• no systemic therapy for colorectal cancer within six months prior to enrolment;

• no contraindications for CRS-HIPEC;

• no previous CRS-HIPEC;

• no concurrent malignancies that interfere with the planned study treatment or the prognosis of resected colorectal PM.

Importantly, enrolment is allowed for patients with radiologically non-measurable disease. The diagnostic laparoscopy/laparotomy may be performed in a referring centre, provided that the peritoneal cancer index (PCI) is appropriately scored and documented before enrolment.

Exclusion criteria

Patients are excluded in case of any comorbidity or condition that prevents safe administration of the planned perioperative systemic therapy, determined by the treating medical oncologist, e.g.:

• Inadequate bone marrow, renal, or liver functions (e.g. haemoglobin <6.0 mmol/L, neutrophils <1.5 x 109/L, platelets <100 x 109/L, serum creatinine >1.5 x ULN, creatinine clearance <30 ml/min, bilirubin >2 x ULN, serum liver transaminases >5 x ULN);

• Previous intolerance of fluoropyrimidines or both oxaliplatin and irinotecan;

• Dehydropyrimidine dehydrogenase deficiency;

• Serious active infections;

• Severe diarrhoea;

• Stomatitis or ulceration in the mouth or gastrointestinal tract;

• Recent major cardiovascular events;

• Unstable or uncompensated respiratory or cardiac disease;

• Bleeding diathesis or coagulopathy;

• Pregnancy or lactation.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-06-2017
Enrollment:	358
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	04-05-2017
Application type:	First submission

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
NTR-new	NL6146
NTR-old	NTR6301

Register ID	
Other	ISRCTN15977568; EudraCT 2016-001865-99; ABR NL57644.100.16 : NCT02758951 Clinicaltrials.gov

Study results

Summary results

Rovers KP, Simkens GA, Punt CJ, et al. Perioperative systemic therapy for resectable colorectal peritoneal metastases: sufficient evidence for its widespread use? A critical systematic review. Crit Rec Oncol Hematol. 2017;114:53-62.