Improving clinical management of colon cancer through CONNECTION, a nation-wide Colon Cancer Registry and Stratification effort.

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Primary objective:Evaluation of the pathological tumour response to neoadjuvant systemic chemotherapy per CMS subtype in patients with microsatellite stable high risk stage II and stage III colon cancer.Secondary Objectives: • Evaluation of the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON53082

Source
ToetsingOnline

Brief title
CONNECTION II

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal therapeutic procedures

Synonym
Colon carcinoma. colon cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Alpe d'Huzes

Intervention

Keyword: CMS, colorectal cancer, neoadjuvant therapy, response

Outcome measures

Primary outcome

The primary endpoint is pathological response according to the tumour response grading (TRG) classification described by Dworak. In the Dworak system, good to complete responders are defined as TRG2+TRG3+TRG4; bad responders are defined as Dworak TRG1+TRG0.

Secondary outcome

• In addition to the primary endpoint, the pathological response will be evaluated per TRG category separately for the different CMS subtypes and per Tumor Regression Score (TRS) following the Modified Ryan scheme (TRS 0, 1, 2, 3). [11]

• Percentages of pathological complete (R0), pathological microscopic incomplete (R1) and pathologically macroscopic incomplete (R2) will be analysed.

• Radiological response after neoadjuvant chemotherapy in relation to CMS subtypes. Radiological response of the tumour will be evaluated by measuring the sum of diameters of the primary tumour, and reported as a continuous outcome measure.

• RFS at two and three years, RFS is defined as the time elapsed between the

diagnosis of the primary tumour and either the date of any recurrence of disease, time of death, or the date of the last follow-up visit at which a patient was considered to have no recurrence.

• Therapy-induced CMS differences. The CMS classification will be performed based on RNA expression profiles.

• Pathologic response will be measured by comparing the pre-treatment biopsies with the resected material by checking regression of Ki-67 (cell cycle) and increased levels of activated Caspase-3 (apoptosis) along with HE staining for cytostatic or cytotoxic effects.

• Prognostic and predictive value of cytotoxic lymphocytes (CytoLym) and cancer-associated fibroblasts (CAF) infiltration scores.

• Evaluation of diagnostic accuracy of ctDNA measurements for monitoring treatment response to neoadjuvant treatment and detection of residual disease.

• Data on surgical complications (i.e. wound infections and anastomotic leak) will be recorded and collected. The complication rate in this study cohort will be compared with the general complication rate of patients who did not receive preoperative chemotherapy, and with the final results of the FOXTROT study.

Exploratory study parameters/endpoints

To optimize the clinical staging of patients with colon cancer, a team of dedicated radiologist will develop a training program for clinical staging of colon cancer on CT-scans. Sensitivity and specificity analyses will be performed on a set of CT-scans of patients within this study and results will analysed before and after completing this training program. All CT-scans will

be analysed by the panel of dedicated radiologist.

An indirect comparison will be made for RFS and OS between the proposed schedule and the standard of care schedule with 4 adjuvant cycles of CAPOX using a control cohort from the Dutch colorectal cancer cohort PLCRC. CT-scans from this cohort will be retrospectively evaluated by dedicated radiologists, who are blinded for outcome, using the CONNECTION-II criteria. Patients with cT3-4N0-2M0 primary colon cancer are eligible for the control cohort. Patients with confirmed microsatellite stable cancer will be included. Data on 2 and 3 years RFS and OS will be collected from the PLCRC database.

Plasma tubes will be collected at four time points, simultaneously with ctDNA collection (before and after 2 courses of neoadjuvant chemotherapy, before surgery and after completing adjuvant chemotherapy). The plasma will be stored for future research purposes to identify novel plasma-derived biomarkers. These markers are easily obtained and might have prognostic and predictive value.

Study description

Background summary

Colorectal cancer is the second most common cancer in the Netherlands with an incidence around 16,000 patients at 2016. Patients with high-risk stage II colon cancer (defined as T4N0) may be offered adjuvant systemic chemotherapy and patients with stage III colon cancer routinely undergo curative surgery combined with adjuvant chemotherapy when fit for treatment. Despite this intensive treatment, 20% of the patients with stage II and 30-35% of the patients with stage III colon cancer will still develop metastatic disease. In addition, on estimate, 50% of the patients with high-risk stage II and stage

III colon cancer would probably never develop metastases after surgery and are therefore over-treated with adjuvant chemotherapy. Furthermore, none of risk factors defining high risk stage II disease seem to have predictive value.
Thus, accurate prognostication and selecting patients for adjuvant chemotherapy is still an unmet need.
The consensus molecular subtypes (CMS) in colorectal cancer, consisting of four molecular subtypes, is currently considered the most robust classification of colorectal cancers with clear distinctive biological features.
It has been suggested that the four subtypes may have prognostic and/or predictive value. Guinney et al. showed a clear relapse free survival and overall survival advantage for CMS1-3 compared to CMS4 based on a patient cohort with stage I to IV colon and rectum carcinoma with divergent therapy strategies.

Although the available evidence does not clearly delineate the predictive and prognostic value of CMS, the biological features of the subtypes and the scarce literature available provide some handles. First, CMS1 tumours, which are generally MSI and hypermutated, show high response to immunotherapy. Second, CMS4 tumours, characterized by a mesenchymal phenotype, seem to have a worse prognosis when compared to CMS1-3. This may be due to biological features resulting in more metastatic potential and/or a poor response to chemotherapy. Roepman et al showed a similar overall survival for patients treated with and without adjuvant chemotherapy for patients with colorectal cancer classified as a mesenchymal phenotype [4]. Last, CMS2 and CMS3 remain subtypes for which the response to chemotherapy is unknown. Recent data however indicate that the response to oxaliplatin is only observed in a fraction of colon cancers, which all belong to the CMS2 subtype. Combined, these observations provide further support for the idea that subtypes might be useful to predict response to chemotherapy.

In de MOSAIC study 2246 patients with stadium II or III colon carcinomas were randomised between adjuvant treatment with 5FU/LV and with 5-FU/LV+ oxaliplatin (FOLFOX-4). The DFS at five and six years postoperatively were both significantly better in the oxaliplatin group compared to the 5FU/LV group ((DFS at 5 years HR 0,80; 95%CI: 0,68-0,93; p=0,003) (OS at 6 years HR 0,84; 95%CI: 0,71-1,00; p=0,046)). In other randomised adjuvant studies, comparable results were found with 5FU/LV or capecitabine in combination with oxaliplatin for stadium II and III colon carcinomas.
The IDEA Collaborative group (International Duration Evaluation of Adjuvant chemotherapy) performed a prospective, pre-planned pooled analysis of 6 concurrently conducted randomised phase III trials to evaluate whether 3 months (3m) adjuvant treatment with FOLFOX/CAPOX is non-inferior 6-months (6m) for DFS. DFS was defined as the time from enrolment to relapse, second CRC, and death (all causes). Non inferiority was to be declared if the 2-sided 95% confidence interval (CI) for DFS hazard ratio (HR 3m v 6m) was below 1.12. The analysis included 12834 patients with stage III colon cancer from 12 countries.
A total of 40% of the patients received CAPOX. Overall, the 3-year DFS rate was

74.6% (3m) and 75.5% (6m), with an estimated hazard ratio (HR) of 1.07 (95%CI, 1.00-1.15). The 3-months versus 6-months DFS HRs were 1.16 (95%CI, 1.06-1.26) and 0.95 (95% CI, 0.85-1.06) for FOLFOX and CAPOX treated patients, respectively. The investigators therefore concluded that while non-inferiority was not established for the overall cohort, non-inferiority of 3-months versus 6-months oxaliplatin-based adjuvant therapy was supported for CAPOX (figure 3). Importantly, grade 3 or higher neurotoxicity was observed less frequently in the 3-months versus 6-months arm (3% vs 16% FOLFOX, 3% vs 9% CAPOX, $p<0.0001$) which showed a benefit for a 3-months regimen. In the Netherlands, approximately 70% of the patients with colon cancer who are offered adjuvant chemotherapy receive CAPOX.

Neoadjuvant therapy has been implemented in the treatment of various GI malignancies including oesophageal, gastric and rectal cancers to 1) to reduce the chance of surgical irradicality, 2) treat microscopic disease that is not addressed by surgery and 3) because patients might better tolerate full intensity chemotherapy when administered prior to surgery rather than postoperatively. Furthermore, neoadjuvant chemotherapy offers the opportunity to evaluate tumour response prior to surgery.
At present, there is very limited data on neoadjuvant chemotherapy in resectable colon cancer patients. Important arguments for the absence of studies on neoadjuvant chemotherapy in resectable colon cancer include amongst others that 1) resectability is seldom an issue, 2) the effect to chemotherapy is uncertain in some patients as discussed above and 3) tumour progression during neoadjuvant chemotherapy might cause bowel obstruction. The FOxTROT Collaborative Group (2012) was the first to set up a trial with neoadjuvant chemotherapy in patients with locally advanced resectable colon cancer and concluded that preoperative chemotherapy was feasible with acceptable toxicity and perioperative morbidity. The results demonstrated that the risk for bowel obstruction was very low with only 1 patient (1%) developing recipient bowel obstruction in the preoperative chemotherapy group.
After this successful pilot study, the FOXTROT study group analyzed the effect of neoadjuvant chemotherapy in more than 1000 patients with colon carcinoma. These results have not yet been published, but they have been presented at the annual ASCO meeting. In this study, patients with a cT3-4N0-2M0 tumor were randomized 2:1 for 3 courses of neoadjuvant and 9 courses of adjuvant FOLFOX or 12 courses of adjuvant FOLFOX. Administering neoadjuvant chemotherapy was safe in accordance with previously presented results with fewer major surgical complications and significant down-staging and reduced risk of incomplete resection. Furthermore the risk of a recurrence after 2 years was smaller in the experimental group (13.6% vs 17.2% HR 0.75 (0.55-1.04), $p = 0.08$).
Thus, neoadjuvant chemotherapy in colon cancer is feasible and suitable to evaluate tumour response. This led us to propose a study to investigate the role of subtypes on therapy response in a novel neoadjuvant setting that allows to determine therapy efficacy of individual colon cancer subtypes.

Study objective

Primary objective:
Evaluation of the pathological tumour response to neoadjuvant systemic chemotherapy per CMS subtype in patients with microsatellite stable high risk stage II and stage III colon cancer.
Secondary Objectives:
• Evaluation of the radiological tumour response to neoadjuvant systemic chemotherapy per CMS subtype.
• Assessment of prognostic value of pathological and radiological response to neoadjuvant systemic therapy for recurrence free survival (RFS) at two and three years and overall survival (OS) at 5 and 10 years.
• Assessment of differences in CMS classification before and after neoadjuvant systemic therapy.
• Assessment of pathological response by Ki-67, Caspase-3 and cystatic-cytotoxic effects on HE-stained tissue slides.
• An indirect comparison will be made for 2 and 3 y RFS and (5 and 10Y) OS between the proposed schedule and the standard of care schedule with 4 adjuvant cycles of CAPOX using a matching control cohort including patients who retrospectively would have been eligible for participation in CONNECTION-IIfrom the Dutch colorectal cancer cohort PLCRC METC-12-510/D. Evaluation of diagnostic accuracy of ctDNA measurements for monitoring treatment response to neoadjuvant treatment and detection of residual disease.
• Results from our study will be compared with the results from the FOXTROT trial

Study design

Prospective multicentre intervention study

Intervention

2 courses neo-adjuvant en 2 courses adjuvant capecitabine and oxaliplatin (CAPOX)

Study burden and risks

As a result of this study, we can possibly prevent a large number of patients from being over-treated or treated insufficiently in the future, and we can look for better and more effective treatment options for patients with poor survival outcome (currently 30% of treated patients). To analyse the predictive value of the CMS subtypes, the response to chemotherapy must be quantified and the most reliable outcome measure is the pathological tumour response. This question can therefore only be answered if we study this in a neo-adjuvant setting.
We expect that patients will have comparable survival benefits compared to

adjuvant chemotherapy, and potentially a subgroup of patients will have an increased survival benefit from participating in this study because of (early) chemotherapy. Most patients in this study would receive the same chemotherapy as standard of care adjuvant treatment instead of neoadjuvant. The regimen used and it*s possible side effects are therefore well known. The side effects to be expected in the neoadjuvant setting are assumed not to differ from those in the adjuvant setting. Plus, patients will probably be in a better physical condition when they undergo the preoperative courses of chemotherapy because they did not undergo surgery yet.
Nevertheless, there are several risks associated with participating in this study and patients should be well-informed on these possible risks. One of the burdens are the side effects of the chemotherapy.
The study population will be treated with 2 courses of neo-adjuvant and 2 courses of adjuvant chemotherapy. According to current guidelines in daily clinical practice, patients with an indication for adjuvant chemotherapy are being offered the same chemotherapy but then 4 courses post-operatively, based on the results of the IDEA study..
This IDEA study, of which the results have been published recently, was a prospective, pre-planned pooled analysis of 6 concurrently conducted randomised phase III trials (n=12,834 patients) to evaluate the non-inferiority of 3 months* adjuvant treatment with FOLFOX/CAPOX compared with 6 months. Based on this study the number of courses of adjuvant chemotherapy in the guideline was adjusted from 8 (6 months) to 4 (3 months). The well known most common side effects for the proposed chemotherapy schedule are peripheral neuropathy, haematological and gastrointestinal side effects, and hand-foot syndrome. By adjusting the number of courses from 8 to 4 on the basis of the IDEA study mentioned above and the current guideline, the load for patients is already considerably less than before. Results from the IDEA study showed that adverse events occurred significantly less often in the 3-months versus 6-months arm [11].
Another potential risk in this study design is progression from disease during the waiting period until surgery. This risk has been investigated in the FOXTROT study. They found that in both the adjuvant chemotherapy group and the neo-adjuvant chemotherapy group one patient needed an acute operation due to bowel obstruction. In addition, one patient in the neo-adjuvant chemotherapy group was found to have metastases. However, it is unlikely that this has been a consequence of postponing surgery due to neo-adjuvant treatment [8]. This conclusion is supported by the fact that in the adjuvant chemotherapy group two patients were found to have peritoneal metastases during surgery. We therefore expect that the chance of progression during the waiting period until the operation is small. However, to monitor this properly, we perform an extra CT scan after 2 courses of neo-adjuvant chemotherapy, in order to adjust the treatment in the event of disease progression. In the FOXTROT study, no differences were seen between the two groups in the duration of admission and side effects of the chemotherapy. Fewer major surgical complications occurred in the preoperative group as well as a reduced risk of imcomplete resection.
Due to erroneously pre-operative staging on CT-scans, there might be patients

with actual pT1-3N0 tumours who will receive chemotherapy in the present study, who would otherwise not qualify for adjuvant chemotherapy according to current standard of care. This will be true for approximately 26% of patients at most, but will most likely be less based on the results of two studies previously performed[12, 13]. However, of these patients, about 10% of patients that are normally not treated with adjuvant chemotherapy do develop recurrent disease for which this chemotherapy could be effective. Moreover, the chemotherapy concerns a maximum of 4 courses in total with limited toxicity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Histologically proven cT3-4, N0-2, M0 primary colon cancer
• >18 years
• Patient is able and willing to provide written informed consent for the

CONNECTION- study
• Informed consent for PLCRC components *clinical data*, *tissue* and *future studies*
• MSS based on pre-treatment biopsy by IHC
• Fit to undergo neoadjuvant chemotherapy and subsequent surgery judged by the primary treating physician
• Adequate full blood count, renal biochemistry and hepatobiliary function

Exclusion criteria

• Any other malignant disease within the preceding 5 years apart from non-melanomatous skin cancer, carcinoma in situ and early stage disease with a recurrence risk <5%
• Colonic obstruction that can not be defunctioned by a stoma
• Patients presenting with a stricturing tumour unable to pass with the scope
• Pregnant or lactating women

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-02-2020
Enrollment:	262
Type:	Actual

Ethics review

Approved WMO

Date:	13-03-2019

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-01-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-12-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-01-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-09-2022
Application type:	Amendment
Review commission:	METC NedMec

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
CCMO	NL62408.041.18