Adjuvant hepatic arterial infusion pump chemotherapy after resection of colorectal liver metastases in patients with a low clinical risk score - a randomized controlled trial

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This study has been transitioned to CTIS with ID 2024-512850-10-00 check the CTIS register for the current data. The primary objective is to compare the efficacy of surgery and adjuvant HAIP chemotherapy to surgery alone in patients with resectable...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52926

Source
ToetsingOnline

Brief title
Adjuvant hepatic arterial infusion pump chemotherapy after resection of CLM

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
Colorectal liver metastases, metastases in the liver of colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Erasmus MC Vriendenfonds;KWF;Erasmus MC Doelmatigheid;Tricumed Medizintechnik GmbH (in kind)

Intervention

Keyword: Colorectal liver metastases, Hepatic arterial infusion pump Chemotherapy, Randomized controlled trial

Outcome measures

Primary outcome

The primary endpoint is progression free survival (PFS).

Secondary outcome

Secondary endpoints include OS, PFS in the liver, postoperative complications,

adverse events, quality of life, and cost effectiveness. Also, the accuracy of

CT angiography to detect extrahepatic perfusion will be evaluated. Next, we aim

to identify predictive biomarkers for the efficacy of HAIP chemotherapy.

Furthermore, the pharmacokinetic profile of intra-arterial administration of

floxuridine will be established.

Study description

Background summary

Colorectal liver metastases
Colorectal cancer (CRC) is the third most common cancer with an annual incidence of 14,000 patients in the Netherlands. More than half of these patients will eventually develop colorectal liver metastases (CLM), of whom 25% have resectable disease at first presentation.(1)

The efficacy of resection of CLM has never been evaluated in a randomized controlled trial (RCT). However, 10-year overall survival (OS) of 20% to 30% has been reported after resection of CLM, which is equivalent to cure.(2) As

compared to resection, systemic chemotherapy alone rarely results in 10-year OS. Complete resection of CLM (with or without ablation), if feasible, is therefore the standard of care. Most patients (up to 80%) develop recurrent disease after curative intent resection of CLM, which in about 50% of patients is confined to the liver.(2) A large phase 3 trial investigating perioperative systemic chemotherapy for patients with resectable CLM found overlapping survival curves after a median follow-up of 8.5 years: 5-year OS was 51% with perioperative chemotherapy versus 48% with surgery alone (p=0.34).(3, 4) This was an unexpected outcome, because systemic chemotherapy is effective in the adjuvant setting for stage III colorectal cancer and in the palliative setting for unresectable stage IV disease. Consequently, better adjuvant treatment is needed.

The risk of recurrence is commonly determined by using the Clinical Risk Score (CRS).(5) The CRS is the sum of five poor prognostic factors: node-positive CRC, disease free interval below 12 months, more than one CLM, largest tumor above 5cm, and serum CEA level above 200 µg/L. More than half of patients with CLM have a low CRS of 0 to 2. The risk of recurrence in these patients is still 70%. No RCT are currently available that demonstrate an improvement of adjuvant chemotherapy certain subgroups of patients. The CRS might be helpful to select patients that benefit from adjuvant chemotherapy after surgical treatment of CLM.

Hepatic arterial infusion pump chemotherapy - Mechanism of action
Hepatic arterial infusion pump (HAIP) chemotherapy for liver tumors is a treatment that has been developed at Memorial Sloan Kettering Cancer Center (MSKCC, New York, USA). It is currently not available in the European Union, because floxuridine is not registered in the EU. The biological rationale for intra-arterial chemotherapy is that the hepatic artery rather than the portal vein is responsible for most of the blood supply to liver tumors.(6, 7) Moreover, up to 95% of drugs such as floxuridine (FUDR) is extracted by the liver during the first-pass, allowing an up to 400-fold increase in hepatic exposure with minimal systemic exposure.(8, 9) Intra-arterial chemotherapy is delivered in the hepatic artery via a surgically implantable pump with a catheter in the gastroduodenal artery. The pump is filled percutaneously and the liver is continuously perfused with chemotherapy for two weeks, which is repeated after a two-week rest period.

Evidence for adjuvant HAIP chemotherapy
Four randomized controlled trials (RCT) have evaluated adjuvant HAI chemotherapy.(10-14) In the first RCT at Memorial Sloan Kettering Cancer Center (MSKCC), patients received adjuvant systemic 5-fluorouracil (5-FU) and HAIP chemotherapy or systemic 5-FU alone. The primary outcome of 2-year survival was 85% with HAIP versus 69% (p=0.02).(10) After a median follow-up of 8.5 years, the median OS was 68 months with HAIP versus 59 months (p=0.10).(10, 13) Median PFS was 31 months with HAIP versus 17 months (p=0.02). Hepatic PFS at 2-years was 85% with HAIP versus 50% (p=0.001).

The second RCT was a multi-site study that found a 4-year recurrence rate of 25% in patients treated with adjuvant HAIP chemotherapy versus 46% without HAIP chemotherapy (p=0.04).(11) A third multi-site RCT used intra-arterial 5-FU instead of floxuridine.(12) The study was closed prematurely when no difference was found at interim analysis. 5-FU has a much smaller first pass effect, resulting in lower tumor exposure and more systemic toxicity. Moreover, an external (rather than implanted) pump was used and many patients had pump failure; 26% never received HAIP chemotherapy in the intervention arm.

Studies from France used intra-arterial oxaliplatin with a percutaneously placed catheter connected to a mediport.(15) This approach has not been evaluated in an RCT. The disadvantage is the much lower first pass effect in the liver of oxaliplatin resulting in lower concentration in the liver tumors and higher systemic exposure and toxicity. Moreover, the mediport doesn*t allow for continuous long-term perfusion.

The NCCN guideline recommends adjuvant HAIP chemotherapy for CLM as an option in experienced centers (Category 2B). Adjuvant HAIP chemotherapy for CLM has not been widely adopted outside MSKCC.(16) Another phase 3 RCT is required to compare adjuvant HAIP chemotherapy for CLM with surgery alone.

A recent retrospective analysis evaluated 2368 consecutive patients undergoing complete resection of CLM with and without adjuvant HAIP chemotherapy at MSKCC between 1992 and 2012.(17) The median OS with HAIP chemotherapy was 67 months versus 44 months without HAIP chemotherapy (p<0.001). After adjusting in multivariable analysis for seven independent prognostic factors including adjuvant modern systemic chemotherapy, the hazard ratio (HR) of HAIP chemotherapy was 0.70 (95% CI: 0.60-0.80, p<0.001).(17) The median OS in the group without HAIP chemotherapy was similar to the 45 months found in a series of 2715 patients from the UK where no HAIP chemotherapy was used.(18) Subgroup analyses of patients with a low CRS (0-2 points) found a median OS with HAIP chemotherapy of 89 months versus 53 months without HAIP chemotherapy (p<0.001). (19)

Safety
HAIP chemotherapy is a complex treatment with a large involved multidisciplinary team. Both subcutaneous placement of the pump and the administration of HAIP chemotherapy itself are complex procedures. Adverse events have been well characterized in the setting of MSKCC.(20)

Imaging to assess adequate perfusion of pump
Prior to the first administration of intra-arterial chemotherapy, bilobar hepatic perfusion and lack of extrahepatic perfusion are confirmed by post-operative technetium-99-labeled macroaggregated albumin (MAA) nuclear medicine scanning. MAA is administered through the IP2000V bolus port. Within 1 hour after MAA injection, a SPECT/CT scan is performed. The total radiation dose of the Tch99 MAA scan is approximately 3-4 mSv. This has been the default

method of imaging in MSKCC.

Concerns with MAA administration are the difficulties in logistics, the low resolution of SPECT imaging, the absences of anatomical information of vascular structures and the possible mismatch between MAA deposition in the liver and distribution of floxuridine during treatment.

Alternatively, CT with contrast injection through the bolus port of an indwelling hepatic catheter provides high resolution information on the anatomy of the post-operative vascular status of the hepatic artery and braches, and the uptake of contrast agent in the liver parenchyma and possible new liver metastases (a pre-treatment CT can therefore be omitted).(21) Using this technique, the distribution of contrast agent is depicted during a specific phase, i.e. a single point in time, without providing information on the dynamic distribution of contrast agent in the liver parenchyma. Previous experience of hepatic perfusion imaging using dual source CT is solely based on the intravenous administration of contrast agents with high flow rates of 4 to 8 ml per second. In this study, contrast agent is administered through the dedicated bolus port of the IP2000V pump while acquiring images using dual source perfusion CT at a temporal resolution of 1.5 second. Because of

Study objective

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The primary objective is to compare the efficacy of surgery and adjuvant HAIP chemotherapy to surgery alone in patients with resectable colorectal liver metastases with a low clinical risk score (CRS 0-2 point). Secondary objectives are to compare postoperative complications, adverse events, quality of life, and costs between the two arms. Another secondary objective is to determine whether CT angiography can replace a nuclear medicine scan to rule out extrahepatic perfusion of the pump. Next, we aim to identify predictive biomarkers for the efficacy of HAIP chemotherapy and study the pharmacokinetic profile of floxuridine.

Study design

A randomized controlled open label, multi-site comparative trial

Intervention

Resection of CLM, pump placement and adjuvant HAIP chemotherapy.

Study burden and risks

Patients in arm A receive the current standard of care, which is resection of the CLM. Burden and risk are the same as with the standard of care, except for filling out quality of life (QoL) questionnaires and additional blood samples (3 time points). All patients are asked to fill out quality of life questionnaires at baseline and 3, 6, 9, 12, 24, and 60 months after surgery. Patients randomized to arm B have a HAI pump surgically implanted placed at the time of resection of CLM. The study intervention comes in addition to the standard of care. Prior to the first administration of HAIP chemotherapy a technetium-99-labeled macroaggregated albumin nuclear medicine scan and a CT angiography are performed to confirm bilobar hepatic perfusion and rule out extrahepatic perfusion. Patients will proceed with 6 cycles of chemotherapy. Follow-up after treatment is identical to the standard of care. Surgical complications related to HAIP pump placement are uncommon (<10%), but include hepatic artery thrombosis, pump pocket infection, pump dysfunction, pump dislocation, and arterial haemorrhage at the site of arterial catheter insertion. The radiation dose of the Tch99 MAA scan is 3-4 mSv. The radiation dose of the CT angiography is 15 mSv, which is comparable to a diagnostic CT of the abdomen. A total of 5-10 ml contrast agent will be infused which with a negligible effect on renal function. HAIP chemotherapy will require two hospital visits for each cycle, with a maximum total of 12 visits. HAIP chemotherapy toxicities include ulcer disease and biliary sclerosis, which can both be largely avoided by imaging prior to treatment and monitoring of liver tests and dosages adjustments, if needed. Systemic side effects with HAIP chemotherapy of floxuridine are rare (<1%). The amount of blood samples that will be taken is for the biomarker study is 20 ml per time point. The number of time points is 3 for patients randomized to arm A (total volume 60 ml), and 5 for patients randomized to arm B (total volume 100 ml). The pharmacokinetic profile of floxuridine will be determined by blood samples drawn during 10 time points in this study in patients randomize do arm B. The amount of blood is 4.5 ml per time point, with a total of 50 ml. The burden and risks associated with taking the amount and number of blood(samples) in this study are negligible. The expected benefit in median OS found in propensity score analysis of more than 2000 patients was 36 months in patients with al low CRS (89 with versus 53 months without HAIP chemotherapy).

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

• Age >= 18 years. • ECOG performance status 0 or 1 • Clinical Risk Score (CRS) of 0-2 • Histologically confirmed colorectal cancer (CRC) • Radiologically confirmed CLM amenable for resection or open ablation • Positioning of a catheter for HAIP chemotherapy is technically feasible based on a CT with early arterial phase with 1mm cuts • Adequate bone marrow, liver and renal function conducted within 15 days prior to inclusion.

Exclusion criteria

• Presence of extrahepatic disease (including positive portal lymph nodes) at the time of liver resection or any time since CRC diagnosis. Patients with small (<= 1 cm) extrahepatic lesions that are not clearly suspicious of metastases are eligible. • Second primary malignancy except in situ carcinoma of the cervix, adequately treated non-melanoma skin cancer, or other malignancy treated at least 5 years previously without evidence of recurrence. • Prior hepatic radiation, resection, or ablation. • CLM requiring two-staged resections. • Liver-first resections. • Postoperative radiation of non-surgically treated (resection or open ablation) CLM • (Partial) portal vein thrombosis.
• Known DPD-deficiency (heterozygous or homozygous) • Pregnant women or lactating women.

• History of psychiatric disability judged by the investigator to be clinically significant, precluding informed consent or interfering with compliance for HAIP chemotherapy. • Serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator. • Organ allografts requiring immunosuppressive therapy.
• Serious, non-healing wound, ulcer, or bone fracture. • Chronic treatment with corticosteroids (dose of >= 10 mg/day methylprednisolone equivalent excluding inhaled steroids). • Serious infections (uncontrolled or requiring treatment). • Participation in another interventional study for CLM with survival as outcome. • Participation in another prospective study with an interventional medical product. • Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-08-2018
Enrollment:	230
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	FUDR
Generic name:	floxuridine

Ethics review

Approved WMO Date:	05-06-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-08-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-08-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-10-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-05-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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: 26427
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EU-CTR	CTIS2024-512850-10-00
EudraCT	EUCTR2018-001696-21-NL
CCMO	NL65956.078.18