Hepatic arterial infusion PUMP chemotherapy combined with systemIc chemoTherapy for potentially resectable colorectal liver metastases

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This study has been transitioned to CTIS with ID 2024-515525-28-00 check the CTIS register for the current data. The aim of this study is to prove feasibility of HAIP chemotherapy (floxuridine) in combination with standard systemic chemotherapy…

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

Summary

ID

NL-OMON55263

Source
ToetsingOnline

Brief title
PUMP-IT

Condition

- Gastrointestinal neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
colorectal adenocarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Medische hulpmiddelen industrie.,Tricumed Medizintechnik GmbH

Intervention

Keyword: Floxuridine, FOLFIRI, FOLFOX, Hepatic arterial infusion pump

Outcome measures

Primary outcome

The primary objective of the study is feasibility of the HAIP chemotherapy and concomitant systemic chemotherapy. We define this combination feasible if at least 70% of the included patients scheduled for surgery can be treated with at least 2 cycles of HAIP chemotherapy combined with systemic chemotherapy.

Secondary outcome

• Safety (surgical complications and chemotherapy toxicity).

• Response rates.

• Progression Free Survival (PFS).

• Overall Survival (OS).

• Conversion rates.

• Quality of Life (QOL).

Study description

Background summary

Current treatment of unresectable CRLM includes subsequent lines of systemic (chemo)therapy aiming to convert the CRLM from an unresectable to a resectable or local treatable state in order to prolong survival. Conversion rates of modern first line systemic chemotherapeutic regimens, as described in multiple

retrospective studies with highly selected patients, are observed in 10-76% of patients, resulting in a 5-year survival of 33-43% after conversion. Patients with progressive disease on first line therapy are offered second line systemic therapy. Conversion during second line systemic therapy is rare and described in only 7-13.5% of patients.These patients have a poor prognosis with a median OS of approximately 10-15 months. However, overall survival (OS) of patients undergoing local treatment after conversion on second line systemic therapy is comparable to what is observed after conversion on first line systemic therapy.

Hepatic arterial infusion pump (HAIP) can deliver high-dose regional chemotherapy to the CRLM using their unique arterial blood supply. Floxuridine is used for HAIP chemotherapy because of the advantages of having a half-life of ten minutes, a 95% first-pass effect and allowing high intrahepatic dosing resulting in increased hepatic exposure by a factor 400, with minimal systemic exposure (e.g. complications). These specific properties of HAIP chemotherapy make it possible to combine high-dose local HAIP therapy with standard of care systemic therapy.
Several single center studies from Memorial Sloan Kettering Cancer Center (MSKCC) (New York, USA) have shown high response rates with HAIP chemotherapy in combination with systemic therapy for unresectable CRLM. Conversion to resection of the initially unresectable CRLM have been observed in up to 57% of chemo-naïve patients and in 20%-38% of patients with prior systemic therapy treated with the combination of HAIP and systemic therapy. Irrespective of conversion, the combined therapy resulted in a median OS of 50.8-76.6 months and a 5-year OS of 51.9% for chemo-naïve patients. The median and 5-year OS was 27.7-35 months and 27.9%, respectively, for patients who have been treated with systemic therapy before.

Although these results are impressive, they come from a single center and have not yet been confirmed elsewhere. Most important reasons were the absence of marketing authorization for FUDR in Europe, the technically challenging surgical procedure of HAIP implantation and the need for stringent monitoring and specific management of HAIP chemotherapy requiring a highly skilled multidisciplinary treatment team.

A study investigating combined treatment is required to prove feasibility in a multicenter setting outside MSKCC before a multicenter randomized phase III trial can be initiated in the Netherlands.

Study objective

This study has been transitioned to CTIS with ID 2024-515525-28-00 check the CTIS register for the current data.

The aim of this study is to prove feasibility of HAIP chemotherapy (floxuridine) in combination with standard systemic chemotherapy consisting of

FOLFOX or FOLFIRI.

Study design

Multicenter, open label, interventional, feasibility study

Intervention

Surgical implantation of HAIP followed by administration of intra-arterial floxuridine (HAIP chemotherapy) to the liver with concomitant standard systemic FOLFOX (5-FU, leucovorin and oxaliplatin) or FOLFIRI (5-FU, leucovorin and irinotecan).

Study burden and risks

High response and conversion rates to locally treatable metastases have been demonstrated in MSKCC. Irrespective of conversion, survival data suggest increase of median survival of patients treated with the combined treatment. These data are single center experience and have not been confirmed elsewhere.

HAIP (chemotherapy) will be added to the standard of care systemic treatment. Prior to HAIP implantation a CT angiography will be performed to conclude sufficient vascular anatomy of the liver when this cannot be concluded from prior imaging. The HAIP willbe implanted surgi-cally and the gallbladder will be removed during this procedure. Surgical complications related to HAIP implantation are uncommon (<10%), and include hepatic artery thrombosis, HAIP pocket infection, and arterial haemorrhage at the site of arterial catheter insertion. Prior to the first administration of HAIP chemotherapy, a technetium-99m-labeled macro-aggregated al-bumin nuclear medicine scan (99mTc-MAA scintigraphy) with or without a CT angiography will be performed to confirm bilobar hepatic perfusion and to rule out extrahepatic perfusion. The effective dose of the 99mTc-MAA scintigraphy and the CT angiography are 3-4 mSv and 15 mSv respectively. A diagnostic CT of the abdomen is approximately 15 mSv.

Patients will proceed with HAIP chemotherapy combined with standard systemic chemotherapy. Administration of HAIP chemotherapy will be scheduled on the same day as systemic chemotherapy administration. HAIP chemotherapy toxicities include ulcer disease and biliary sclerosis, which can both be largely avoided by imaging prior to treatment, monitoring of liver tests and early FUDR dose adjustments. Systemic side effects of HAIP chemotherapy are rare (<1%) and therefore suitable for combination with systemic treatment.

Systemic chemotherapy can be continued after HAIP chemotherapy discontinuation. After HAIP chemotherapy discontinuation the pump can be surgically removed with a simple procedure if desired by the patient however, the attached catheter

into the hepatic artery will re-main in situ. Follow-up after HAIP chemotherapy is similar to standard of care. After conversion surgery, standard follow-up protocol for postoperative patients after liver surgery will be followed, independent of the numbers of cycles of FUDR.

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Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

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.
• Life expectancy of at least 12 weeks.
• Histologically confirmed colorectal adenocarcinoma

• Indication for first or second line systemic therapy, confirmed in a multidisciplinary meeting.
• Potentially resectable (i.e. unresectable and upfront resectable CRLM with indication for neoadjuvant systemic therapy), confirmed in a multidisciplinary meeting and radio-logically on (PET) CT thorax/abdomen and/or MRI obtained <= 4 weeks prior to regis-tration.
• Positioning of a catheter for HAIP chemotherapy is technically feasible confirmed in the multidisciplinary liver meeting based on imaging. The default site for the catheter insertion is the gastroduodenal artery (GDA). Accessory or aberrant hepatic arteries are no contra-indication for catheter implantation. The GDA should have at least one branch to the liver, accessory or aberrant hepatic arteries should be ligated to allow for cross perfusion to the entire liver through intrahepatic shunts.
• Indication and eligibility for abdominal surgery confirmed in a multidisciplinary meet-ing, e.g. primary tumour resection, stoma revision/reversal and diagnostic surgery.
• In case of primary tumour in situ: tumour should be (potentially) resectable, confirmed in a multidisciplinary meeting.
• Adequate bone marrow, liver and renal function as assessed by the following laborato-ry requirements to be conducted within 15 days prior to inclusion.
o Hb >= 5.5 mmol/L
o Absolute neutrophil count (ANC) >=1.5 * 109/L
o Platelets >=100 * 109/L
o Total bilirubin < 1.5 mg/dL
o ASAT <= 5 * times the upper limit of normal (ULN)
o ALAT <= 5 * ULN
o Alkaline phosphatase <= 5 * ULN
o (estimated) glomerular filtration rate (eGFR) > 45 ml/min.
• Before patient registration, written informed consent must be given and signed accord-ing to ICH-GCP, and national/local regulations.

Exclusion criteria

• Extrahepatic metastases. Confirmed with CT thorax/abdomen obtained <= 4 weeks prior to registration. Patients with small (<= 1 cm) extrahepatic lesions that are not clearly suspicious of metastases are eligible.
• Prior hepatic radiation, resection (other than biopsy), or ablation.
• Concurrent malignancies that interfere with the planned study treatment or the prog-nosis of CRLM.
• Participation in other clinical trials interfering with the study treatment as judged by the treating physician.
• Dihydropyrimidine dehydrogenasedeficiency (DPD deficiency).
• Pregnant or lactating women.
• Serious concomitant systemic disorders that would compromise the safety of the pa-tient 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).
• History of psychiatric disability judged by the investigator to potentially hamper com-pliance with the study protocol and follow-up schedule.
• Any psychological, familial, sociological or geographical condition potentially hamper-ing compliance with the study protocol and follow-up schedule.
• Pregnant or lactating women.
• 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.
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Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-09-2020

Enrollment:	31
Type:	Actual

Medical products/devices used

Generic name:	Implantable (hepatic) arterial infusion pump
Registration:	Yes - CE outside intended use
Product type:	Medicine
Brand name:	5-fluorouracil
Generic name:	5-fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	FUDR
Generic name:	Floxuridine
Product type:	Medicine
Brand name:	Irinotecan
Generic name:	Irinotecan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Leucovorin
Generic name:	Folinic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Oxaliplatin
Generic name:	Oxaliplatin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-07-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-09-2020

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-08-2022
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
EU-CTR	CTIS2024-515525-28-00
EudraCT	EUCTR2019-003260-44-NL
CCMO	NL70112.031.19