A Randomized phase III trial comparing hepatic arterial injection of Yttrium-90 resin microspheres (SIR-spheres) plus systemic maintenance therapy versus systemic maintenance therapy alone for patients with unresectable liver metastases from colorectal cancer which are controlled after induction systemic therapy: the SIR-step trial

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We propose to conduct a randomised phase III trial evaluating a maintenance strategy comparing hepatic arterial injection of Yttrium-90 resin microspheres plus continuing simplified chemotherapy with/without targeted therapy (bevacizumab, or...

Ethical review	Approved WMO
Status	Pending
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON42551

Source
ToetsingOnline

Brief title
the SIR-step trial

Condition

- Metastases

Synonym
metastatic colorectal cancer; liver disease

Research involving
Human

Sponsors and support

Primary sponsor: UZ Antwerpen
Source(s) of monetary or material Support: Research grant by Sirtex,Sirtex

Intervention

Keyword: Liver, Metastatic Colorectal Cancer, Radioembolisation

Outcome measures

Primary outcome

Primary end-points:

- Time to first progression (TTP1 overall)

Secondary outcome

Secondary end-points:

- Time to global progression (TTP1 + TTP2), Time to second progression (TTP2),

TTP1 liver only

- Progression Free Survival (PFS)

- Overall Survival (OS)

- Safety

- Ro resection rate

- Quality of Life

Exploratory analysis:

- Prediction and evaluation of SIR-Spheres treatment response (only for Belgian

centres)

Study description

Background summary

Zie protocol pagina 9-10

Study objective

We propose to conduct a randomised phase III trial evaluating a maintenance strategy comparing hepatic arterial injection of Yttrium-90 resin microspheres plus continuing simplified chemotherapy with/without targeted therapy (bevacizumab, or cetuximab or panitumumab) versus continuing simplified chemotherapy with/without targeted therapy (bevacizumab, or cetuximab or panitumumab) alone for patients with liver only or liver dominant unresectable mCRC with controlled disease (SD or PR according RECIST1.1 criteria) after 3 to 6 months of chemotherapy induction. The aim of the study is to investigate whether an intensified maintenance treatment consisting of SIRT + simplified maintenance chemotherapy has a benefit in terms of time to progression (TTP) compared to simplified chemotherapy maintenance alone, in patients with controlled disease after 3 to 6 months of induction therapy.
We would like to demonstrate the feasibility and safety of this approach and to investigate if this strategy has the potential to increase the outcome of the patient.

Study design

Design of the study
Chemonaive patients with exclusive or dominant unresectable liver metastases from CRC will be identified at diagnosis for potential inclusion in the study. After 3 to 6 months of chemotherapy induction +/- targeted therapy, patients will be screened and tumor response assessed. Patients presenting controlled disease (partial response or stable disease according to RECIST1.1 (30)) and persistent unresectable metastatic liver disease will be eligible for trial inclusion. The timing between the last cycle of the induction chemotherapy and trial inclusion must not exceed 6 weeks. In order to facilitate the screening procedure and inclusion of the patient in the trial and avoid chemotherapy

interruption or inadequate timing before enrollment of the patient (see inclusion criteria), it is highly recommended to perform a disease evaluation every 2 to 3 months during the induction treatment period.
Liver unresectability would be determined at diagnosis and subsequently in the disease evolution by an experienced liver surgeon in a multidisciplinary meeting. Resectability means the potential complete surgical clearance (+/- radiofrequency ablation) of all detectable liver lesions with tumor-free margins and compatible with an adequate hepatic reserve. Practically, bilateral tumor location, number and location of lesions, and inadequate hepatic reserve remains the main decisional factors. The possibility of a two-stage hepatectomy is left at the discretion of the investigator.
At inclusion, patient will be randomized between a hepatic arterial injection of Yttrium-90 (HAI-90Y) resin microspheres plus continuation of 5FU/LV with/without targeted therapy based on previous use as part of induction therapy, or continue 5FU/LV with/without targeted therapy alone until progression. Groups will be stratified according to previous use of targeted therapy and oxaliplatin or/and irinotecan-based chemotherapy (induction chemo), and the presence or absence of extra-hepatic metastases.
For response evaluation, whole body enhanced spiral CT-scan will be performed every 2-3 months. In an exploratory analyses and for Belgian selected centres only (optional) , FDG-PET scan will be performed at baseline, at week 6-8 and 12-14 post start of maintenance treatment to assess metabolic response. At progression, according to RECIST 1.1 criteria, oxaliplatin or irinotecan will be reintroduced depending on its previous use during the induction chemotherapy treatment. In case oxaliplatin cannot be reintroduced (persistent neurotoxicity) second line chemotherapy will be mandatory. If oxaliplatin and irinotecan are used concomitantly (triplet regimen), choice of chemo scheme reintroduction is left to investigator*s decision.

Study entry is defined as the date that the randomization has been done. No patient may enter the study without signing the informed consent document. The screening period is defined as the period before inclusion when the patient meets the eligibility criteria to be included in the trial. Subjects are randomized after all eligibility criteria have been confirmed. A subject is considered to be randomised into the study once a subject identification number has been assigned to the subject. In order to be considered eligible for the study, patients must fulfil the inclusion and exclusion criteria specified in 3.3 below.

Study design and defined end-point is summarized in figure 1, protocol page 11.

Intervention

ARM A: Modified LV5FU2 as described below (6.2.1) D1-2 +/- bevacizumab 5 mg/kg over 30 min or +/- cetuximab 250 mg/m² weekly or 500 mg/m² biweekly or +/- panitumumab 6 mg/kg (according its previous use) every 2 weeks.
ARM B: HAI-90Y radioembolization (SIR-spheres injection) + modified LV5FU2 +/-

bevacizumab 5 mg/kg over 30 min or +/- cetuximab 250 mg/m² weekly or 500 mg/m² biweekly or +/- panitumumab 6 mg/kg according its previous use as described in arm A.

Study burden and risks

Described in Dutch (above)

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Willing and able to provide written informed consent
2. Histologically confirmed adenocarcinoma of the colon or rectum, with or without primary

tumour in situ. Unequivocal and measurable (RECIST 1.1) CT evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent at the time of trial entry.
3. Partial response or stable disease (RECIST 1.1 criteria, controlled metastatic disease) after chemotherapy induction with oxaliplatin and/or irinotecan- based induction chemotherapy (doublet or triplet combinations) +/- targeted therapies during 3 to 6 months.
4. Trial inclusion must be performed between 3 and 6 months since the date of the first course of chemotherapy (induction) administration.
5. Limited extra-hepatic metastases in the lung and/or lymph nodes are permitted. Metastases in the lung must either be not more than five nodules in number with no nodule more than 1 cm in diameter or 1 single lesion of up to 1.7 cm in diameter. Involvement of lymph nodes in 1 single anatomic region (pelvis, abdomen or chest) are permitted provided their longest diameter measures less than 2 cm.
6. All imaging evidence used as part of the screening process must be within 28 days prior to randomisation.
7. Suitable for either treatment regimen as determined by clinical assessment undertaken by the Investigator.
8. Patients may have received adjuvant chemotherapy or (neo-) adjuvant chemo-radiotherapy to the pelvis, provided the last dose of chemotherapy was administered at least 6 months prior to begin chemotherapy induction. Previous radiotherapy to the pelvis is not an exclusion criterion.
9. WHO performance status 0 * 1
10. Adequate haematological, renal and hepatic function as follows:
Haematological
Neutrophils > 1.5 x 109/L
Platelets > 100 x 109/L
Renal
Creatinine < 1.5 x ULN
Hepatic
Bilirubin 1.0 X ULN
Albumin * 30 g/L
ALT 5.0 x ULN
AST 5.0 x ULN
LDH 2.5 x ULN
The date of blood tests must be within 28 days prior to randomisation.
11. Aged 18 years or older.
12. Female patients must either be postmenopausal, sterile (surgically or radiation- or chemically-induced), or if sexually active using an acceptable method of contraception.
13. Male patients must be surgically sterile or if sexually active and having a pre-menopausal partner must be using an acceptable method of contraception.
14. Life expectancy of at least 3 months without any active treatment

Exclusion criteria

1. Evidence of ascites, cirrhosis, portal hypertension, main portal venous tumour involvement

or thrombosis as determined by clinical or radiologic assessment.
2. More than 6 weeks since the last chemotherapy administration before trial inclusion.
3. Previous radiotherapy delivered to the upper abdomen.
4. Non-malignant disease that would render the patient unsuitable for treatment according to this protocol.
5. Prior major liver resection: remnant liver < 50% of the initial liver volume. Patient with a biliary stent can be included.
6. Liver tumor involvement > 80% before study inclusion (not at diagnosis but when trial inclusion for the patent is planned).
7. Resectable metastatic disease at trial inclusion.
8. Progressive disease during first-line metastatic chemotherapy. Adjuvant chemotherapy for colorectal cancer is not an exclusion criterion provided that it was completed more than 6 months prior to start of 1st line therapy.
9. No oxaliplatin or irinotecan use during the first 3 to 6 months induction chemotherapy.
10. Pregnant or breast feeding.
11. Concurrent or prior history of cancer other than adequately treated non melanoma skin cancer or carcinoma in situ of the cervix
12. Severe allergy to non-ionic contrast agents which would prevent contrast media use during the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	16-12-2015
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Generic name:	SIR-spheres microspheres
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	03-03-2017
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	01895257
CCMO	NL55801.058.15