Evaluation of Sorafenib in combination with local micro-therapy guided by Gd-EOB-DTPA enhanced MRI in patients with inoperable hepatocellular carcinoma

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Treatment strategy in early HCC aims at the local removal of the tumor and represents a potentially curative treatment option (resection, liver transplantation, PEI, RFA, BT). Patients in intermediate and advanced stage of HCC receive treatment with...

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

Summary

ID

NL-OMON41292

Source
ToetsingOnline

Brief title
SORAMIC

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
hepatocellular carcinoma; liver cancer

Research involving
Human

Sponsors and support

Primary sponsor: Otto-von-Guericke-Universität

Source(s) of monetary or material Support: Ministerie van OC&W,Bayer,Sirtex Medical , Walter-Flex-Strasse 2 , Bonn, DE 53113

Intervention

Keyword: Inoperable hepatocellular carcinoma, local micro-therapy, Primovist enhanced MRI, Sorafenib

Outcome measures

Primary outcome

Primary objectives

1. In patients in whom local ablation therapy is appropriate (local ablation group), to determine if the sorafenib in combination with tumor ablation (RFA) prolongs the time-to-recurrence (TTR) in comparison with RFA + placebo.

2. In patients in whom RFA is NOT appropriate (palliative treatment group), to determine if the combination of yttrium-90 microspheres (SIRT) + sorafenib improves the overall survival (OS) in comparison to sorafenib alone.

3. T o confirm in a 2-step procedure that Primovist®-enhanced MRI is non-inferior (first step) or superior (second step) compared with contrast-enhanced multislice CT for assignment of patients to a palliative vs. local ablation treatment strategy.

The overall study is successful if the primary objectives 1 OR 2 are met AND Primovist®-enhanced MRI is at least non-inferior to contrast-enhanced CT for treatment decisions.

Secondary outcome

Secondary objectives

1.To assess health-related quality of life

2.To compare the number of detected lesions and the diagnostic confidence in

Primovist-enhanced MRI with contrast-enhanced CT

3.To compare Primovist-enhanced MRI with contrast-enhanced CT regarding the

detection of recurrence (patients in the local ablation study group only)

4.To assess the safety of the combination of RFA + sorafenib in comparison to

RFA + placebo

5.To assess the safety of the combination of SIR-Spheres and sorafenib therapy

in comparison to sorafenib therapy alone

6.To assess in the palliative study group overall survival separately for

patients with and without portal thrombosis

Study description

Background summary

Primary hepatocellular carcinoma (HCC) is the fifth most common cancer in the world, with over 1.25 million cases of HCC occurring annually. HCC is a leading cause of cancer-related mortality in both men and women worldwide with an increasing incidence rate and a predominance in developing countries. Only about 30% of patients are diagnosed early enough to benefit from potentially curative therapies, such as surgical resection, allogeneic liver transplantation or percutaneous ablation, which afford 5-year survival rates of 50-75 %.
Median survival in the absence of treatment is 3-6 months; actuarial survival is 31% at one year, 8% at two years, and <3% at three years in the USA (SEER1). Most HCC patients are diagnosed at intermediate to advanced stages of disease, for which no generally accepted standard therapy exist, apart from sorafenib. HCC generally leads to death as a consequence of local tumor growth, tissue destruction and liver destruction, rather than widespread extrahepatic disease. Once a diagnosis has been made, patient prognosis varies according to disease stage and treatment received. The main prognostic factors are related to tumor status (defined by the number and size of nodules, the presence or absence of vascular invasion, and the presence or absence of extrahepatic spread), liver function (defined by Child*Pugh class, serum bilirubin and albumin levels, and portal hypertension), and general health status (defined by Eastern Cooperative Oncology Group [ECOG] classification and presence of symptoms). Etiology is not an independent prognostic factor.

Several classification systems are available for HCC. The Barcelona Clinic Liver Cancer (BCLC) classification has emerged during recent years and has been used to link stage stratification with a recommended treatment strategy, and to define a standard of care for each tumor stage. Depending on tumor stage, different treatment options are available: local surgical resection, orthotopic liver transplantation, percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), brachytherapy (BT), and transarterial chemoembolization (TACE). Recently, the multikinase inhibitor sorafenib and Selective Internal Radiation Therapy (SIRT) have shown promise in advanced liver cancer.

Study objective

Treatment strategy in early HCC aims at the local removal of the tumor and represents a potentially curative treatment option (resection, liver transplantation, PEI, RFA, BT). Patients in intermediate and advanced stage of HCC receive treatment with palliative intent (TACE, sorafenib, SIRT). It is the goal of this study to examine in a *real world setting* the prospects of two treatment options: sorafenib as an adjuvant therapy after local tumor resection for patients with early HCC, and SIRT as an option for patients with advanced HCC. The selection of an appropriate treatment for individual patients depends largely on the number and size of liver lesions. Diagnostic imaging using CT and MRI plays a major role in this respect. In the past several years, the liver-specific MR contrast agent Primovist has received marketing authorization throughout (most of) Europe for the detection and characterization of liver lesions. In a diagnostic sub-study, Primovist-enhanced MRI will be compared with contrast-enhanced CT with regard to the detection of liver lesions, appropriate assignment to treatment group (local ablation or palliative), and the detection of tumor recurrence.

Study design

Randomized, multi-center
Patients with a diagnosis of hepatocellular carcinoma will receive either
* local ablation therapy of liver lesions by radiofrequency ablation followed by sorafenib or placebo (local ablation group), or
* radioembolization (SIRT) + sorafenib or sorafenib alone (palliative treatment group).
In each study group, patients will be randomized to one of the 2 treatment arms following a pre-defined randomization plan. Randomization will be on a 1:1 basis in the local ablation group and on the basis of 10 (sorafenib only) : 11 (SIRT + sorafenib) in the palliative treatment group.
Patients in the local ablation group will be followed at 2 months intervals for recurrence and overall survival, patients in the palliative treatment group will be followed for overall survival. Follow-up in each study group will end 24 months after inclusion of the last patient into the respective study group.

The assignment of patients to the local ablation or palliative study group will be based on the ablative potential of RFA (local ablation if *4 tumors, each *5 cm in size). Diagnostic imaging will be used to guide this decision. The assignment to the local ablation or the palliative treatment group will be made by the local investigator.
As a sub-study, all patients will undergo Primovist®-enhanced MRI in addition to contrast-enhanced CT before assignment to one treatment group. The goal of the sub-study is to assess the value of Primovist®-enhanced MRI to correctly stratify patients for a local ablation or palliative treatment strategy. Primovist®-enhanced MRI will be compared with contrast-enhanced multislice CT using a truth panel assessment as the standard of reference. In addition, Primovist-enhanced MRI and contrast-enhanced CT will be obtained during follow-up of patients in the local ablation group to assess its potential for detection of recurrence.

Intervention

SIRT (palliative arm)
One SIRT prescription consists of the pre-treatment assessment followed by one or 2 treatment sessions.
The aim of pre-treatment assessment of the hepatic arterial vasculature is to ensure delivery of the microspheres to the target. It consists of a detailed hepatic and visceral angiography together with the assessment of the hepatic-pulmonary shunt fraction. In angiography, the superior mesenteric, celiac and hepatic arterial branches are evaluated and parasitic supply to tumor nodules via non-hepatic vessels is excluded. Evaluation includes a determination of the arterial location and any consequent necessity for coil-embolization of the gastroduodenal artery, right gastric artery and any other accessory arteries to prevent inadvertent administration of microspheres into the gastrointestinal tract or pancreas. In addition, parasitic extrahepatic supply should be coil-embolized.
The presence of variant hepatic arterial anatomy may alter the treatment plan. Treatment with SIR-Spheres® microspheres is precluded by stenosis or slow antegrade flow within the hepatic arteries that results in embolic occlusion of the vessel and, therefore, reflux into extrahepatic territories.
Hepatopulmonary shunting secondary to tumor-related pathologic arteriovenous pathways, as well as reflux toward the gastrointestinal region, may be detected in scintigraphy with the injection of 148 MBq (4 mCi) of 99mTc-MAA as a SIR-Spheres® microspheres surrogate into the hepatic arterial territory (scintigraphy is to be performed after embolization of vessels, if applicable).
The regions of interest are the counts from the lungs and from the liver.
Patients in whom the shunt fraction indicates potential exposure to the lung to an absorbed radiation dose of more than 30 Gy should be excluded from treatment with SIR-Spheres® microspheres.
Patients who are randomized to receive SIRT but who are not regarded as eligible for SIRT after the pre-treatment assessment will be switched to the sorafenib only arm within the palliative treatment group.

SIRT will be administered in 1 or 2 treatment sessions, depending on the involvement of the liver lobes. The study procedure guide will contain further instructions on the dosing of SIR-Spheres and the treatment procedure.

Sorafenib (curative and palliative arm)
As adjuvant treatment 400mg BID versus placebo, in the curative setting as well as in the palliatieve setting sorafenib 400mg BID.

RFA (for the curative arm
A maximum of 2 percutaneous RFA sessions (maximum of 2 weeks apart) is permitted per patient with a maximum of 2 liver lesions treated in each RFA session. Randomization to sorafenib or placebo is performed after completion of RFA.
Percutaneous RFA is to be performed according to the manufacturer*s instructions and following as far as possible routine procedures of the participating hospital. Applicators should be selected according to the size, location, and configuration of the lesion(s) to be treated. Typically, RFA will be performed under conscious sedation, general anesthesia is permitted. After local anesthesia of the site of puncture, the applicator is positioned in the center of the lesion using ultrasound-, CT- or MR-guidance. The success of ablation is to be controlled directly after RFA using ultrasound (preferably contrast-enhanced ultrasound), contrast-enhanced CT, or MR imaging. If for any reason RFA is deemed incomplete within the immediate follow-up (up to 2 weeks after the initial ablation), RFA is to be repeated once (in this case, the total (maximum) number of RFA sessions will be three).
The study procedure guide will contain further instructions for RFA.

Study burden and risks

The expected side-effect profiles of sorafenib, SIR-Sphere therapy, and the MR contrast agent Primovist® are summarized in the study protocol section 8.7.2.4. Overall, the benefit-risk ratio of the SORAMIC trial is regarded as positive and acceptable.

Local ablation group. This study includes patients with early and advanced HCC. Patients with early HCC (up to 4 liver lesions of a maximum of 5 cm each) will be assigned to the local ablation group. In this treatment group, patients will receive local ablation therapy followed by sorafenib or placebo. Local ablation therapy with RFA represents an accepted treatment option and does not constitute a deviation from routine clinical care. The addition of sorafenib as an adjuvant treatment after local ablation (as planned in this study in half of the patients assigned to the local ablation group) is currently not part of clinical care. Sorafenib treatment in these patients is expected to be associated with adverse events comparable to published data (the incidence of treatment-related adverse events was 80% in the sorafenib arm in the SHARP trial, compared to 52% in the placebo arm, see [26]). In the SHARP trial, adverse events that were more common in the sorafenib arm than in the

placebo arm (e.g., diarrhea, weight loss, and hand*foot skin reaction) were mainly mild to moderate in severity. The two most relevant grade 3 drug-related adverse events were diarrhea and hand-foot skin reaction (both of which occurred in 8% of patients in the sorafenib arm). The overall incidence of serious adverse events from any cause was similar in the two study arms: 52% (153 patients) in the sorafenib arm and 54% (164 patients) in the placebo arm [27].

In case of adverse events, the sorafenib dose can be reduced in this study according to the scheme outlined in the study protocol section 5.5.1. The expected rate and intensity of adverse events is regarded as acceptable because sorafenib is expected to exhibit anti-tumor efficacy and to prolong time-to-recurrence after local ablation therapy. The SORAMIC trial design is expected to provide relevant data regarding the treatment efficacy of sorafenib in the adjuvant situation. Patients of the local ablation group who receive sorafenib may have a personal benefit from participation in this trial. Given the potential beneficial adjuvant treatment effect of sorafenib and the potential personal benefit of participating patients, the benefit-risk ratio of the local ablation treatment group is regarded as acceptable and positive.

Patients of this study group may stay in the study at an average of 16 months. In this case an average of 7 follow up visits and a final visit may be conducted. These visits consist of the following procedures: laboratory assessment (blood samples 18mL and optional additional 12.5mL), ECOG performance status, Quality of life questionnaire and imaging (contrast-enhanced CT and Primovist-enhanced MRI).

Palliative study group. Patients with advanced HCC who are not eligible for the local ablation study group, will be subjected to the palliative treatment group. All patients in this group will receive sorafenib. Sorafenib has been approved for the treatment of hepatocellular cancer and is the standard of care in advanced HCC (see also [28]). The administration of sorafenib in the palliative group of this study, therefore, does not represent a deviation from routine clinical care.

SIR-Spheres therapy is currently not routinely performed in patients with advanced HCC. Half of the patients included in the palliative study group will be randomized to SIR-Spheres therapy before start of sorafenib treatment. These patients may suffer adverse events from the application of SIR-Spheres and from the combined effects of SIR-Spheres and sorafenib.

Current knowledge about the frequency and the severity of adverse events after SIR-Spheres treatment is summarized in section 8.7.2.4. In this study, SIR-Spheres treatment will be adapted to the total tumor load of the liver to reduce the probability of adverse events (see Table 5 in the study protocol section 5.5.3). Treatment of the whole liver in one session will not be allowed, two separate lobar treatment sessions are required in the case that

the whole liver needs to be treated. This careful sequential approach of SIR-Spheres therapy for patients requiring whole liver treatment is expected to significantly reduce the frequency of adverse events. In addition, the DSMB will carefully assess the course of the first patients receiving SIRT in the palliative treatment group. To protect patients participating in this study, the DSMB may recommend changes in the timing of the start of sorafenib treatment (e.g., start of sorafenib treatment later than 3 days after the last SIRT session), or may even recommend to stop this study arm because of adverse events (see study protocol section 8.9, *stopping rule*).

Patients receiving SIRT in the palliative treatment group are expected to have personal benefit and a longer overall survival than patients in the sorafenib-only arm. Considering the expected survival benefit and the measures planned to reduce the probability for severe and serious adverse events (incl. installation of a DSMB), the benefit risk ratio of the palliative study group is regarded as acceptable and positive.

Patients of this study group may stay in the study at an average of 13 months. In this case an average of 6 follow up visits may be conducted. These visits consist of the following procedures: laboratory assessment (blood samples 18mL and optional additional 12.5mL), ECOG performance status and Quality of life questionnaire. Imaging in this study group is in discretion of the investigator and will include contrast-enhanced CT and Primovist-enhanced MRI.

Diagnostic Sub-Study. All patients will undergo contrast-enhanced CT and Primovist-enhanced MRI before being assigned to the local ablation or palliative study group. Patients of the local ablation study group will be followed up with contrast-enhanced CT and Primovist-enhanced MRI at 2-months intervals until recurrence. Contrast-enhanced CT for treatment selection and follow-up in HCC is regarded as standard of care. Primovist-enhanced MRI is an additional diagnostic procedure in the context of this clinical study. There are very few risks associated with MRI scans. The changing radiofrequencies and magnetic fields theoretically can produce heat, but this is not known to be associated with relevant side effects. The risk of the injection of MR contrast agents is considered to be low. Patients with an increased risk of Primovist-associated adverse events are not allowed to enter this study (e.g., patients with a history of allergic reactions, patients with severe renal dysfunction).

Patients participating in this trial may have a personal benefit from Primovist-enhanced MRI (more accurate assessment of disease, earlier detection of tumor recurrence). Considering the potential personal benefit and the low probability for severe and serious adverse events, the benefit risk ratio of the diagnostic sub-study is regarded as acceptable and positive.

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

1. Age: 18-85 years
2. Hepatocellular carcinoma
3. If extrahepatic metastases: liver-dominant disease
4. Stage BCLC A, B, or C
5. Child-Pugh A, Child-Pugh B up to 7 points
6. Willing to comply with all study procedures
7. Has voluntarily given written informed consent

Exclusion criteria

1. If female, pregnant or breast feeding (females of child-bearing potential must use adequate contraception and must have a negative pregnancy test performed within 7 days prior to inclusion into this study)
2. If male, not using adequate birth control measures
3. One or more of the following:
- Hemoglobin <10g/dL,
- WBC <2,500 cells/mm3,
- ANC <1,500 cells/mm3,
- platelets <50,000/mm3,
- ECOG performance status >2
4. Life expectancy <16 weeks or medically unstable
5. Pulmonary metastases
6. Patients with known GFR <30 mL/min/1.73m2
7. PT-INR/PTT >1.5 times the upper limit of normal
8. uncontrolled infections at the time of microtherapy
9. Child-Pugh score >7 points;
10. Uncontrolled ascites
11. tumor load of the whole liver >70%
12. Contraindications for study medications according to product labeling or procedures
13. Having undergone surgical procedures with resection of the sphincter of Oddi
14. Significant cardiovascular disease; e.g., myocardial infarction within 6 months of inclusion, chronic heart failure (New York Heart Association class III or IV), unstable coronary artery disease
15. Uncontrolled hypertension
16. Thrombotic or embolic events including transient ischemic attacks within the past 6 months (tumor-related portal vein thrombosis allowed in the palliative part of the trial)
17. History of GI bleeding within 30 days before inclusion into this study
18. History of esophageal varices bleeding which has not been controlled by effective therapy and/or therapy to prevent bleeding recurrence
19. Previous malignancy other than carcinoma in situ of the skin or the cervix uteri within 5 years prior to inclusion
20. History of organ transplant (including prior liver transplantation)
21. HIV, congenital immune defect, any immunosuppressive therapy for autoimmune disease (rheumatoid arthritis) or inflammatory bowel disease
22. Mental conditions rendering the subject incapable to understand the nature, scope, and consequences of the trial
23. Close affiliation with the investigational site; e.g. first-degree relative of the investigator.
24. Participating in another therapeutic clinical trial or has completed study participation in another therapeutic clinical trial within 30 days of enrolment into this trial
25. Having been previously enrolled in this clinical trial

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-06-2011
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	Sir-Spheres therapy
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Nexavar
Generic name:	Sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Primovist
Generic name:	Gd-EOB-DTPA
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	05-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2009-012576-27-NL
ClinicalTrials.gov	NCT01126645

Register	ID
CCMO	NL32649.018.10