Transarterial Chemoembolization with Drug-Eluting Beads (standard arm) versus Stereotactic Body Radiation Therapy (experimental arm) for hepatocellular carcinoma: A multicenter randomized phase II trial *The TRENDY trial*

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To assess the time to progression after TACE-DEB and after SBRT in a comparable population of patients diagnosed with HCC.

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

Summary

ID

NL-OMON44103

Source
ToetsingOnline

Brief title
TRENDY trial

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
hepatocellular carcinoma, primary liver cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: KWF

Intervention

Keyword: (SBRT), hepatocellular carcinoma, randomized phase II, stereotactic body radiation therapy, transarterial chemoembolization (TACE-DEB)

Outcome measures

Primary outcome

The primary endpoint of this study will be time to progression, defined as time

from randomization to radiological progression.

Secondary outcome

Secondary endpoints will be:

-Time to local recurrence

-Response rate (complete and partial response)

-Overall survival

-Toxicity

-Quality of life.

Study description

Background summary

Primary liver cancer, particularly hepatocellular carcinoma (HCC) is a major health problem. Curative therapies for HCC are considered hepatic resection, liver transplantation and radiofrequency ablation (RFA). Hepatic resection is preferred for patients with limited disease, non-cirrhotic livers or selected patients with Child-Pugh A cirrhosis. Unlike resection, liver transplantation

treats the tumor and the underlying cirrhosis present in the liver. Candidates for liver transplantation are preferably those with cirrhosis and tumors that comply with the Milan criteria (single tumor <5cm or 1-3 tumors each of * 3cm). Because most patients are not amenable to resection or liver transplantation, RFA has emerged as an effective treatment option. RFA is limited by the location of the tumor in the liver and by the tumor size with best results after RFA achieved for tumors
*3cm. For patients that are not eligible for RFA due to large or multifocal tumors, transarterial chemoembolization with drug- eluting beads (TACE-DEB) is the preferred treatment. Stereotactic body radiation therapy (SBRT) delivers a highly effective dose of irradiation to the tumor while maximally avoiding dose delivery to surrounding healthy structures. SBRT is offered as an ablative local treatment with reported high percentages of complete and partial responses with limited toxicity. An international expert committee on HCC has recommended time to progression (TTP) as primary endpoint for phase II randomized trials. Although data is scarce the best published median TTP after TACE-DEB was 16 months and after SBRT 36.5months in a more or less comparable patient population (Barcelona Clinic Liver Cancer stage system A-C).
To our knowledge this trial will be the first in the world to compare TACE-DEB and SBRT. This trial may have a big impact on the control of the disease and may contribute to change the standard of care from a palliative to a more radical/curative intention in this patient population

Study objective

To assess the time to progression after TACE-DEB and after SBRT in a comparable population of patients diagnosed with HCC.

Study design

Randomized, prospective, and phase II study.

Intervention

Patients with HCC will be randomized to receive the standard treatment, TACE-DEB loaded with doxorubicin or the experimental arm, SBRT.

Study burden and risks

Data regarding toxicity after TACE-DEB provide evidence of a relatively safe treatment. Most complications are only minor with an increase in transaminase levels and total bilirubin.
Previous experience with SBRT in HCC patients has been reported in several papers with high rates of local tumor control and limited toxicity.
Expected risk of hepatic toxicity or radiation induced liver disease with the SBRT protocol used in this trial is expected to be * 5%. Radiation-induced

liver disease will be defined as anicteric ascites and elevation of alkaline phosphatase levels to at least two fold above the pretreatment values in absence of tumor progression. The bleeding risk in patients with portal hypertension is expected to be low. In fact only patients with a limited risk of bleeding will be considered for this study.
Other organs at risk constraints comply with international accepted recommendations. The expected associated toxicity as perforation for stomach, esophagus and bowel is low. Risks associated to fiducial marker implant are also limited. The most important is the risk of intrahepatic bleeding. In order to minimize this risk of complications, the implant will be carried out by trained interventional radiologists. The patient will remain hospitalized during 4-5 hours after the implant.

No DSMB will be installed due to the minimal risk associated with the participation in this study. No interim analysis is planned for this study.

Radiological endpoints will be centrally reviewed by an independent radiologist

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

-Patients diagnosed with HCC (follow the diagnostic algorithm recommended by the EASL*EORTC Clinical Practice Guidelines 2012). The treatment can be delivered prior to liver transplantation.
-Barcelona Clinic Liver Cancer Stage System class A-B
-One to three tumors with at most up to a cumulative diameter of * 6 cm measured in all 3 axes. In case of multiple lesions, the most favorable setting would be that all are eligible for TACE-DEB. If only one or two lesions are eligible for TACE-DEB, and the others are eligible for ablation, the patient can still be included in the study. Satellite nodules count as independent lesions.
-Earlier treatments with ablation are allowed until a maximum of 3 lesions, including the one, or ones, that will be randomized in the study. Lesions previously treated with ablation should not have exceeded a diameter of 3cm.
-Measurable disease on CT/MRI-scan, according to mRECIST criteria for HCC within 6 weeks prior to randomization
-Tumor visibility on CT
-None or cirrhosis Child-Pugh A
-Age * 18 years
-ECOG performance status 0-1
-Albumin> 28 g/l, bilirubin < 50 µmol/l, INR < 2.3, AST/ALT < 5 times ULN, within 6 weeks prior to randomization
-Platelets will be preferable * 50x10E9/ l (if not, thrombocytes transfusion is allowed to ensure a safe procedure at the discretion of the interventional radiologist and gastroenterologist). Leukocytes > 1.5x10E9/l, Hb > 6 mmol/l, within 6 weeks prior to randomization
-Written informed consent
-Willing and able to comply to the follow-up schedule
-Planned to start treatment within 6 weeks from randomization.

Exclusion criteria

-Eligibility for resection or RFA
-More than three tumors in the liver
-Ascites
-Any signs of acute viral or non-viral hepatitis
-Encephalopathy
-Vascular tumor invasion (contact with the vessel will not be considered contraindication).

-Previous radiotherapy to the liver
-Known current pregnancy
-Distance from the tumor to the esophagus, stomach, duodenum, small bowel or large bowel < 0.5 cm on CT or on MRI (randomization imaging).
-Uncontrolled portal hypertension (high bleeding risk). If gastroscopy has been performed, untreated esophageal varices grade III or IV.

Study design

Design

Study phase:	2
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):	01-05-2015
Enrollment:	64
Type:	Actual

Medical products/devices used

Generic name:	DC Bead Drug delivery Embolisation System
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	17-04-2015
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-02-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2016
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: 28819
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL51318.078.14
OMON	NL-OMON28819