Identification of predictive factors for response to neo-adjuvant Sunitinib in patients with resectable hepatocellular carcinoma

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To identify predictive factors for response to sunintib treatment in patients with HCC. By discovering changes in pathways involved in HCC carcinogenesis due to sunitinib treatment in tissue/biomarkers and to correlate these changes to FDG-PET scan…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON32387

Source
ToetsingOnline

Brief title
Predictive factors of response to Sunitinib in HCC.

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary therapeutic procedures

Synonym
hepatocellular carcinoma, liver cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W,Pfizer

Intervention

Keyword: functional imaging, hepatocellular carcinoma, predictive factors, Sunitinib

Outcome measures

Primary outcome

to determine changes (tissue/serum biomarkers) in familiar pathways of

hepatocellular cancer (HCC) to sunitinib treatment

Secondary outcome

-to correlate the changes in these pathways to FDG-PET scan and 111In-

bevacizumab scan results before and after sunitinib treatment

-to assess the safety and toxicity of pre-surgery sunitinib in patients with

liver-only HCC

Study description

Background summary

Hepatocellular carcinoma(HCC) is the fifth most common malignancy in the world. The incidence of HCC is still rising. The only cure for HCC is surgical resection or livertransplantation. Unfortunately most patients more than 80% of the patients present with unresectabel or advanced disease, with the majority of patients dying within 1 year after diagnosis.

Partial liver resection can be performed in patients with a preserved liver function. This is often not the case in patients with HCC with cirrhotic livers. Radiofrequency Ablation (RFA) is a treatment modality which has emerged as a technique applicable in patients in whom partial liver resection is not possible or is contraindicated because of an expected high operative risk. Also, in patients in whom a liver transplantation is scheduled, RFA is used a bridge to transplantation.

To improve outcome after RFA or partial liver resection neoadjuvant therapie might be an option. In metastatic HCC tyrosine kinase inhibitors have showed improvement in overall survival. Sunitinib is an orally administered, small molecule inhibitor of multiple receptor tyrosine kinases implicated in tumor growth, angiogenesis, and metastatic progression.

The problem with response assessment in HCC with conventional imaging is to differentiate between benign or malignant disease, especially in patients with cirrhosis who have regenerating nodules and fibrosis. With new agents like tyrosine kinase inhibitors the problem with conventional imaging is that usually responses involve central necroses that does not involve the outside borders for some period of time. Therefore in patients with GIST and kidney cancer who are treated with tyrosine kinase inhibitors response evaluation is best done using 18F-FDG PET scanning. In contrast with the tumors mentioned above, in patients with HCC FDG PET scans are positive in only 60% of cases. This may be related to a more aggressive feature of the tumor compared to negative scans due to inherent differences or stage of the tumor. Because of these considerations evaluation of sunitinib response in HCC patients with FDG PET scans next to conventional imaging seems useful.

Over-expression of VEGF occurs in many human tumor types, also in hepatocellular carcinoma. VEGF production by the tumour will result in abundant presence of VEGF in the micro-environment of the tumour. Non-invasive assessment of VEGF-levels in the micro-environment of the tumour could guide in the development and follow up of anti-VEGF targeted therapy. Currently, we are evaluating the pharmacokinetics, biodistribution and tumour uptake of 111In-bevacizumab in patients. If scanning with 111In-bevacizumab leads to adequate imaging of tumours and assessment of VEGF levels in the tumour, this technique may be used to assess tumour response in the future of anti-angiogenic therapy.

Study objective

To identify predictive factors for response to sunintib treatment in patients with HCC. By discovering changes in pathways involved in HCC carcinogenesis due to sunitinib treatment in tissue/biomarkers and to correlate these changes to FDG-PET scan and 111In- bevacizumab scan results before and after sunitinib treatment.

Study design

Patients who are planned for RFA or partial liver resection will be treated neo-adjuvant with sunitinib.

Before start and between day 18-21 a FDG-PET scan will be performed.

Four weeks before surgical resection, patients receive an i.v. injection of 111In-bevacizumab. Gamma-camera imaging will be performed on day 0, 2 , 4 and 7 post injection (The optimal time to scan the patients will be determined after two or three patients. Hereafter patients will only be scanned once or twice after tracer injection, most likely on day 0 and 4 after tracer injection.)
After the first series of scans, patients will be treated with sunitinib One week before RFA or surgical resection, patients receive another dose 111In-bevacizumab (100mBq). Gamma-camera imaging will be performed on day 0, 2, 4 and 7 post injection (The optimal time to scan the patients will be determined after two or three patients. Hereafter patients will only be scanned once or twice after tracer injection, most likely on day 0 and 4 after tracer injection) and before surgical resection.

After neoadjuvant treatment with sunitinib, the tumor is biopsied either during open surgery (resection or RFA) or during CT guided percutaneous RFA.

The tumour activity, anti-angiogenic and apoptotic response of sunitinib will be determined by evaluating histological, haematological parameters and FDG-PET and 111In- bevacizumab respons.

Intervention

Patients will be treated with a daily dose of 37.5 mg sunitinib for 21 days until 48 hours before RFA or partial liver resection.

Study burden and risks

Any toxicity will be scored according to the Common Toxicity Criteria version 3.0.
Sunitinib
Sunitinib administration will start 23 days before partial liver resection or RFA and will be cessitated 2 days before partial liver resection or RFA. In case of grade 3/4 toxicity treatment is withheld until grade 2 toxicity. Dose reduction of 12.5 mg is recommended based on individual safety and tolerability.A dose reduction for sunitinib should be considered if sunitinib must be co-administered with a strong CYP3A4 inhibitor. Although Sunitinib is a FDA/EMEA approved compound for metastatic renal cell carcinoma and GIST its use in combination with RFA has never been tested. However major operations seem to be safe when performed 48 hours after cessitation of Sunitinib. However since we do not know the exact effect of Sunitinib on wound healing and liver regeneration in case of partial liver resection or RFA procedure we have chosen a cautious study design and will include only one patient at a time in the study.

Radiolabeled 111In-bevacizumab
In this study bevacizumab is administered in a tracer-dose. The risk of any

additional side effects by the administration of a tracer dose (10 mg) will be very low, compared to therapeutic administration of bevacizumab (375-600 mg). Administration of 111In-bevacizumab entails radiation load from the participating patients. It has been calculated that a dose of 100 Mbq will lead to a radiation load of 18mSv. In this study protocol this will lead to 36 mSv. For comparison, a CT-abdomen will lead to a radiation dose of 10-15 mSv. The poor prognosis of thos patient group (5 year survival: in case of RFA before liver transplantation 70%, in case liver transplantation is not possible, but only RFA or partial liver resection 40 %) and the potential new information given by the study makes this radiation loas acceptable.

FDG PET scan
There will be an additional radiation dose of 7 mSv due to the FDG PET scan.

Liver biopsy
The risk of performing a biopsy of an HCC is considered to be small, with an overall reported complication rate of less than 0.2%. Potential risks are bleeding, arterioportal shunts and needle tract seeding. The risk of needle tract seeding is estimated to be between 0.6 and 5.1%. In two studies no needle tract seedings were found in 433 and 101 tumor biopsies respectively. The use of a guiding needle introducer (as is current standard in the UMCG) which is not in contact with the tumor itself protects the tract from tumor cell deposition, even if the cutting needle (which enters the tumor) contains tumor cells at its outer side.

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

-Histologically proven and documented hepatocellular carcinoma of the liver
-Liver-only HCC eligible for RFA and/or resection
-Age >= 18
-WHO performance status 0-2
- Adequate bone marrow, liver and renal functions
-Written, voluntary informed consent
-Patients must be accessible to follow up and management in the treatment centre
-Patients must sufficiently understand the Dutch language and must be able to sign the informed consent document.
-A life expectancy of at least 3 months.

Exclusion criteria

-Extrahepatic metastases or intrahepatic metastasis not eligible for RFA/resection
-CHILD C liver cirrhosis
-Patients with evidence or a history of bleeding diathesis
-Clinically significant cardiovascular disease
-Evidence of serious active infections
-Prior chemotherapy or biological therapy for metastatic disease.
-Prior radiotherapy on the involved area.
-Major surgery within 28 days before the initiation of the study.
-Dementia or altered mental status that would prohibit the understanding and giving of informed consent
-Pregnant or lactating women. Sexually active patients of childbearing potential must implement effective contraceptive practices during the study when treated with sunitinib.
-CNS metastases (CT-Scan not mandatory)
-Treatment with any investigational drug within 30 days before the start of the study
-Prior allergic reaction to immunoglobulins or immunoglobulin allergy

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	111In-Bevacizumab
Product type:	Medicine
Brand name:	Sutent
Generic name:	Sunitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2008-002397-34-NL
Other	n.a.
CCMO	NL23010.042.08