A Phase I safety, toxicity and biomarker study of peri-operative sorafenib treatment in patients undergoing radiofrequency ablation (RFA) for liver metastases of colorectal cancer

Published: 27-05-2008
Last updated: 10-08-2024

- To asses the safety and toxicity of peri-ablative sorafenib given in doses of either 200 mg or 400 mg twice daily.- To asses the effect of perioperative sorafenib on the RFA induced mobilization of endothelial progenitor cells and cytokines...

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

Summary

ID

NL-OMON31730

Source
ToetsingOnline

Brief title
Peri-ablative Sorafenib in patients with CRLM

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Miscellaneous and site unspecified neoplasms benign
- Hepatobiliary therapeutic procedures

Synonym
Liver cancer, Liver neoplasm

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Antiangiogenesis, Colorectal Cancer, Liver Tumours, Radiofrequency ablation

Outcome measures

Primary outcome

Safety/ Toxicity:

The complication rate of the combination of sorafenib and RFA should not exceed the summarized complication rate of RFA. Toxicity analysis will be based on dose limiting toxicities (DLT*s) considered to be related to sorafenib treatment. RFA-related toxicities are registered in the UMC Utrecht RFA database.

Dose limiting toxicities (DLT*s) attributed to the combination of sorafenib and RFA are defined as grade 3 or 4 neutropenia and thrombocytopenia longer than 7 days; febrile neutropenia grade 3 or 4; non-hematological toxicities grade 3 or 4 (excluding ALAT and ASAT levels, alopecia and non pre-medicated nausea/vomiting)

Liver failure: Grade 3 / 4 liver function impairment or any other grade 4 toxicity (toxicities are graded according to the CTC version 3.0)

Efficacy:

Pharmacodynamic assessment: determination of the number of endothelial progenitor cells and cytokines involved in angiogenesis before, during and

after RFA.

Secondary outcome

Disease free survival (DFS) after the combination of perioperative sorafenib

and RFA

Study description

Background summary

Colorectal cancer is the second leading cause of cancer related deaths in the western world with it*s incidence still rising. Death from colorectal cancer is caused by metastatic disease rather than by the primary tumour (Boyle et al, 2004; Ponz de Leon et al, 2004). About 50% of patients with colorectal cancer are destined to develop hepatic metastases. Liver surgery offers the only hope for cure for colorectal liver metastases with a 5 year survival rate between 20-50%. Unfortunately, only 20% of patients are eligible for partial liver resection due to localization, number or size of the metastases or insufficiënt hepatic parenchymal reserve. Patients with non-resectable or non-resected liver metastases of colorectal cancer survive for only 8-12 months without any treatment. Median overall survival after radiofrequency ablation (RFA) is 30 months. Local tumor destruction by RFA has emerged as a safe and effective treatment modality for patients with colorectal liver metastases that are irresectable. RFA is a technique in which heat is locally generated leading to tumour destruction with only minimal concomitant damage to surrounding liver parenchyma. RFA is considered a safe technique with the ability to accomplish local disease control as shown in a large population of patients. The overall survival is between 40 and 53% at 3 years. Reported complication rates range from 7.1 to 9.8% The overall survival is between 40 and 53% at 3 years. A downside of RFA is the recurrence rate , with local recurrence rates varying from 0 - 60% A hypoxic microenvironment, generated by RFA, seems to be an ideal microenvironment for tumor cells to grow In ischemic tissue, HIF-1alpha is stabilized which induces tumor neovascularization through upregulation of VEGF (Carmeliet et al, 1998; Brahimi-Horn et al, 2001). VEGF is one of the most potent downstream effectors of HIF 1-alfa and plays a pivotal role in the stimulation of hypoxia driven angiogenesis. Angiogenesis is a prerequisite for metastatic progression. The aim of this study is to incorporate the VEGFR inhibitor sorafenib in the treatment with RFA. Cancer progression greatly depends on the formation of new blood vessels in order to supply the tumor of oxygen, nutrients and growth factors (Zhang Y, 2007; Folkman et al, 2002). Furthermore, it facilitates tumour dissemination. Neovascularization can occur by proliferation of endothelial cells, or by mobilization of bone

marrow-derived endothelial progenitor cells, which migrate and incorporate into growing vessels (Ribatti, 2004). In 9 patients treated with RFA that were in included in the UMC Utrecht liver database we found a rise in the number of EPC*s as soon as 2 hours RFA treatment. (Nijkamp et al, unpublished observations)

Study objective

- To asses the safety and toxicity of peri-ablative sorafenib given in doses of either 200 mg or 400 mg twice daily.
- To asses the effect of perioperative sorafenib on the RFA induced mobilization of endothelial progenitor cells and cytokines involved in the process of angiogenesis
-To assess the effect of perioperative sorafenib on DFS after RFA.

Study design

This is a phase I study to assess the safety and toxicity of peri-ablative sorafenib treatment. Furthermore, this study will assess if peri-opertive sorafenib administration prevents mobilization of bone marrow derived endothelial progenitor cells as a result of radiofrequency ablation (RFA) for patients with liver metastases of colorectal cancer.

Patients must fulfill all the inclusion/exclusion criteria to be eligible for the study.
Sorafenib treatment will start 7 days before RFA by taking sorafenib 200 mg tablets twice daily.

Cohort 1: Sorafenib: dose level 200 mg (1 tablet) twice daily until progression occurs or until 6 months of treatment, whatever occurs first.
Cohort 2: Sorafenib: dose lever 400 mg (2 tablets) twice daily until progression occurs or until 6 months of treatment, whatever occurs first
Blood collection for measurement of EPC*s and cytokines will be done pre-sorafenib treatment, pre-ablative treatment, 20 min, 2, 4, 24 hours after RFA.
CT chest, 4 phase CT abdomen will be made before RFA, 2 weeks after RFA, thereafter
every 6 months after RFA. This is the standard follow up after RFA

Cohort 1 and 2 can be extended until 12 patients if advense events occure which are not related to Sorafenib or RFA. The Principal Investigators will decide whether cohorts wil be extended and report this to the Medical Ethical Committee of the UMC Utrecht.

Intervention

Radiofrequency ablation

Study burden and risks

Liver regeneration and wound heeling.
Both VEGF receptor 2 (VEGFR2) and VEGFR1 mediate functions on endothelial cells and other cell types that mediate wound heeling and liver regeneration.
There are no clinical studies reporting the effect of sorafenib on wound heeling and liver regeneration. In a preclinical study where PTK/ZK, a compound that inhibits all VEGF receptors was administered to mice before and after RFA, there were no problems with wound heeling and liver regeneration encountered (vd Bilt et al. 2006 unpublished results)
Tetrogenicity:
Sorafenib is an antiangiogenic compound that in animal studies has shown to be highly teratogenic and to induce embryo fatal toxicity. Therefore only patients using an effective method of birth control will be included.
Adverse events:
Most common side-effects of sorafenib are: hand-foot skin reaction and rash, usually limited to grade 1 and 2.
Hypertension: blood pressure should be monitored the first 6 weeks.
Most reported side effects in clinical studies were mild to moderate and manageable.
Gastrointestinal perforation is a very uncommon event, occurring in less than one percent of patients. Haemorrhage: An increased risk of bleeding is reported. The incidence of grade 3 and 4 bleeding events is 2% for patients treated with sorafenib compared to placebo.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
3584 CX Utrecht
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
3584 CX Utrecht
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients that have signed written informed consent
2. Patients undergoing percutaneous or laparascopic radiofrequency ablation for colorectal liver metastases, i.e., patients with metastases limited to the liver that are not surgically resectable.
3. Patients of whom their largest liver metastasis does not exceed 4 cm.
4. Patients with metastases that are not adjacent to or incorporated in one of the large vessels or biliary tract
5. Patients with metastases > 1 cm distance from the liver hilus.
6. Patients with 3 metastases or less
7. Age > 18 years.
8. ECOG Performance Status of 0 tm 2.
9. Life expectancy of at least 12 weeks.
10. Subjects with at least one uni-dimensional(for RECIST) or bi-dimensional (for WHO) measurable lesion. Lesions must be measured by CT-scan or MRI
11. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to screening:
12. No concurrent chemotherapy or other anti-tumour therapies.

Exclusion criteria

1. Extrahepatic metastases
2. WHO performance status > 2
3. Patients undergoing open RFA
4. Patients should not have more than 3 metastases
5. Largest lesion should not exceed 4 cm
6. Patients should not have any tumour adjacent to or incorporated in one of the large vessels or bile structures

7. Patients should not have any tumor situated in less than 1 cm of the liver hilus.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-04-2009
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sorafenib
Generic name:	Nexavar
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-05-2008
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-11-2008
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	14-08-2009
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
EudraCT	EUCTR2007-007001-73-NL
CCMO	NL21093.041.07