Neo-adjuvant dovitinib in patients with hepatocellular carcinoma prior to local treatment: a phase II study

Published: 30-08-2011
Last updated: 29-04-2024

Introduction of dovitinib in the neo-adjuvant setting, can provide both clinical informationabout it*s activity in patients with HCC (reduction of tumor size, influence on the tumor bloodflow as assessed by CT perfusion imaging) and (histo-)...

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

Summary

ID

NL-OMON35941

Source
ToetsingOnline

Brief title
Neo-adjuvant dovitinib in HCC

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
hepatocellular carcinoma, liver cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: dovitinib, hepatocellular carcinoma, neo-adjuvant, phase II

Outcome measures

Primary outcome

1. Toxicity and Safety of dovitinib (all grades, and grade 3 or 4 toxicities).

2. Tumor response according to RECIST criteria (version 1.1) after 4 weeks of

treatment as

determined by CT-imaging and changes in intratumoral blood flow as measured by

CT

perfusion imaging.

3. Histopathology of HCC specimens obtained following 4 weeks of treatment with

dovitinib

(comparison with pre-treatment biopsy, parameters: e.g. tumor necrosis,

percentage of vital

tumor cells, vascular density).

Secondary outcome

1. Progression free survival of local relapse.

2. Immunohistochemistry: changes in FGFR1, FGFR2, FGFR3, FGFR4, bFGF, FGF19,

HGF,

PLGF, cleaved caspase-3, Ki-67, CD31, pERK, M30/M65, and correlation with

clinical data.

3. Changes in plasma levels of VEGF, basic FGF, soluble VEGFR1, soluble VEGFR2,

FGF2,

FGF23, FGF19, HGF, cKit, and inhibition of ERK (extracellular receptor kinase)

phosphorylation in PBMC*s (pre-treatment, day 15, day 26, and 1 month after

local

treatment) and correlation with clinical data.

Study description

Background summary

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and eighth most common cancer in women worldwide. An estimated 748,000 of new cases are diagnosed annually (2008). HCC is most prevalent in sub-Saharan Africa, Southeast Asia and the Amazon basin, with more than half of the patients being reported in China. In Western countries HCC is much less frequent. Worldwide, the estimated 5-years survival rate is about 7% and 698,000 deaths annually are attributed to HCC (2008). The majority of HCC patients (>80%) present with advanced or irresectable disease. At the time of diagnosis, in 75% of patients, HCC tumors are multifocal in the liver.
Cure and long-term survival of patients with HCC is only achieved in patients in whom radical local therapy can be achieved. Surgical resection is possible in only 5% of patients, and in these patients the 5-year survival rates vary from 40% to 90%. In general, patients with a solitary HCC of less than 5 cm, or multiple lesions confined to one liver segment or to the left liver lobe, without vascular invasion, in the presence of well-preserved hepatic function, have the best outcomes. Orthotopic liver transplantation can be considered in patients with one tumor less than 5 cm or up to 3 tumors, all less than 3 cm. These HCC patients have survival rates similar to those patients who undergo liver transplantation for end-stage liver disease in the absence of HCC, with 5-year survival rates of 75%.
In recent years, minimal invasive local ablation modalities with radiofrequency

thermal
energy (RF ablation) and (chemo)embolization have been introduced, also leading to 5-yeas
survival rates of more than 40%. Such local therapy modalities are more frequently applied in
recent years in the *pre-transplantation setting* in order to bridge the time interval to liver
transplantation in those HCC patients, who fall within the accepted criteria for liver
transplantation, since the waiting time until a suitable liver becomes available may reach a
period of up to 2 years.
Neo-adjuvant systemic therapy has been widely used in order to increase the success rate of
local treatments of primary tumors by down-staging of the primary tumor and eradication of
occult distant metastases. There is sufficient evidence for its efficacy in many types of cancer,
(e.g., breast cancer, ovarian cancer, various gastrointestinal tumors), thus translating this into
current standard practice in these tumors, but until recently no such clear evidence was found
in HCC. This is related to the lack of sensitivity of HCC to the traditionally used
chemotherapy and hormonal therapy.
In recent years several agents have been developed which have promising activity in the
highly vascularized hepatocellular carcinomas, interacting with pivoting cellular pathways in
the growth and proliferation of HCC. Targets include the receptors of Vascular Endothelial
Growth Factor (VEGF), Platelet Derived Growth factor (PDGF), Epidermal Growth Factor
(EGF), hepatocyte growth factor (c-Met), and the Insulin-like Growth Factor (IGF), and
signal transduction pathways responsible for the proliferation, invasion, metastasis, or
survival of tumor cells such as the Raf/MEK/ERK, P13K/Akt/mTOR route, and Jak/Stat
signaling pathway. Sorafenib, a multikinase tyrosine kinase inhibitor of the Raf
serine/threonine kinases and the VEGFR1-3, PDGFR-beta, c-Kit (stem cell factor receptor),
and p38 tyrosine kinases, is until now the only agent proved to prolong survival of patients
with advanced HCC. Many clinical trials have been initiated with various other TKI*s and
other novel biological agents, which have interactions with pivoting cellular

pathways in the
growth and proliferation of HCC, such as the mTOR inhibitor everolimus (RAD001), the
VEGFR inhibitor bevacizumab, and the multikinase inhibitors sunitinib and brivanib.
The multikinase inhibitor Dovitinib targets VEGFR1-3, PDGFR-beta, FGFR1-3, FLT-3 (FMS-like tyrosine kinase-3), cKIT, Ret (glial cell-line derived neurotrophic factor receptor),
TrkA (nerve growth factor receptor), and csf-1 (macrophage-colony stimulating factor
receptor) RTK*s. Most of these targets play an important role in the growth and proliferation
of HCC. Therefore Dovitinib is a very promising agent in the treatment of HCC.

Study objective

Introduction of dovitinib in the neo-adjuvant setting, can provide both clinical information
about it*s activity in patients with HCC (reduction of tumor size, influence on the tumor blood
flow as assessed by CT perfusion imaging) and (histo-) immunological information about its
activity against HCC, as can be assessed at the time of local treatment. Furthermore, novel
targeted therapy is until now almost exclusively used in patients with advanced HCC who are
generally in a worse clinical condition than patients eligible for local therapy and who may
have tumors with different biological characteristics than in an earlier phase of their disease.
Therefore, this study could provide specific information about the efficacy and tolerability of
targeted therapy with dovitinib in a new subset of patients.

Study design

This is an open-label phase II trial investigating clinical activity and safety of Dovitinib in
patients with HCC prior to local therapy.

Patients will be treated with Dovitinib 500 mg/day orally during 5 days a week for a total
period of 4 weeks, where after any form of local resection will be performed.

Intervention

Patients will be treated with Dovitinib 500 mg/day orally during 5 days a week for a total
period of 4 weeks, where after any form of local resection will be performed.

Study burden and risks

Study assessments will be performed at screening, week (W) 2 day (D) 1 (optional), W3D1, W4D1 (optional), W4D5, 1 month after local treatment. Patients will receive dovitinib 5 days a week during 4 weeks or until unacceptable toxicity, death or discontinuation from the study for any other reaseon.

Risks:
- Toxicity due to the use of dovitinib (especially nausea, fatigue, diarrhea and vomiting)
- Reaction to the use of contrast fluid (used for CT/MUGA scans)
- Side effects of blood sampling.

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. Histological or cytological confirmed HCC or HCC diagnosed by the Barcelona criteria.
2. HCC stage A or B according to the Barcelona Clinic Liver Cancer (BCLC) staging classification (appendix 2; Llovet et al, 2008a).
3. Patients eligible for local therapy, i.e. RF-ablation, chemo-embolization, or surgical resection
4. ECOG (WHO) performance status 0, 1, or 2
5. Age >= 18 years old
6. At least one uni-dimensional measurable lesion. Lesions must be measured by CT-scan or MRI-scan
7. Patients must have adequate bone marrow, liver and renal function as assessed by the following laboratory requirements:
• Absolute neutrophil count (ANC) >= 1.5 x 109/L
• Platelets >= 75 x 109/L
• Hemoglobin (Hgb) >= 6.0 mmol/L
• Serum total bilirubin: <= 1.5 x ULN
• Child-Pugh score of up to 6 points, i.e. Child-Pugh classe A (appendix 3), with no encephalopathy. Child-Pugh status must be calculated based on clinical findings and laboratory results during the baseline/screening period
• ALT and AST <= 3.0 x ULN (with or without liver metastases)
• Serum creatinine <= 1.5 x ULN or serum creatinine >1.5 - 3 x ULN if calculated creatinine clearance (CrCl) is >= 30 mL/min using the Cockroft-Gault equation, see formula below:
CrCl = [140-age (years)] x weight (kg) / [72 x serum Cr (mg/dL)]
(if patient is female multiply the above by 0.85)
8. Life expectancy of at least 3 months
9. Patients who give a written informed consent obtained according to local guidelines

Exclusion criteria

1. Patients with brain metastases or who have signs/symptoms attributable to brain metastases and have not been assessed with radiologic imaging to rule out the presence of brain metastases
2. Patients with another primary malignancy within 3 years prior to starting study drug, with the exception of adequately treated in-situ carcinoma of the uterine cervix, skin cancer (such as basal cell carcinoma, squamous cell carcinoma, or non-melanomatous skin cancer), or superficial bladder tumors (Ta, Tis, and T1)
3. Patients who have received the last administration of an anticancer therapy including

chemotherapy, immunotherapy, hormonal therapy and monoclonal antibodies (but excluding nitrosurea, mitomycin-C, targeted therapy and radiation) <= 4 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
4. Patients who have received the last administration of nitrosurea or mitomycin-C <= 6 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
5. Patients who have received targeted therapy (e.g. sunitinib, sorafenib, pazopanib) <= 2 weeks prior to starting study drug, or who have not recovered from the side effects of such therapy
6. Patients who have had radiotherapy <= 4 weeks prior to starting study drug, or <= 2 weeks prior to starting study drug in the case of localized radiotherapy (e.g. for analgesic purpose or for lytic lesions at risk of fracture), or who have not recovered from radiotherapy toxicities
7. Patients who have undergone major surgery (e.g. intra-thoracic, intra-abdominal or intra-pelvic), open biopsy or significant traumatic injury <= 4 weeks prior to starting study drug, or patients who have had minor procedures, percutaneous biopsies or placement of vascular access device <= 1 week prior to starting study drug, or who have not recovered from side effects of such procedure or injury
8. Patients with any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
• Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
a. History or presence of serious uncontrolled ventricular arrhythmias
b. Clinically significant resting bradycardia
c. LVEF assessed by 2-D echocardiogram (ECHO) < 50% or lower limit of normal (which ever is higher) or multiple gated acquisition scan (MUGA) < 45% or lower limit of normal (which ever is higher)
d. Any of the following within 6 months prior to starting study drug: myocardial infarction (MI), severe/unstable angina, Coronary Artery Bypass Graft (CABG), Congestive Heart Failure (CHF), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), Pulmonary Embolism (PE)
e. Uncontrolled hypertension defined by a SBP >= 160 mm Hg and/or DBP >= 100 mm Hg, with or without anti-hypertensive medication(s)
• Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of dovitinib (e.g. ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
• Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
• Patients who are currently receiving anticoagulation treatment with therapeutic doses of warfarin
• Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol
9. Pregnant or breast-feeding women
10. Women of child-bearing potential, who are biologically able to conceive, not employing two forms of highly effective contraception. Highly effective contraception (e.g. male condom with spermicidal jelly, foam suppository or film, diaphragm with spermicide) must be used by

both sexes during the study and must be continued for 8 weeks after the end of study treatment. Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study. Women of child-bearing potential, defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months), must have a negative serum pregnancy test <= 14 days prior to starting study treatment and must use two forms of highly effective contraception (also applicable to their partners who are biologically able to conceive).
11. Fertile males not willing to use contraception, as stated above
12. Patients unwilling or unable to comply with the protocol

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-05-2012
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TKI258
Generic name:	onbekend

Ethics review

Approved WMO Date:	30-08-2011
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-10-2011
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
EudraCT	EUCTR2011-002445-36-NL
CCMO	NL36964.058.11