A phase 2a study on the anti-tumoral effect of cannabis oil (THC 10% / CBD 5%) in patients with untreatable advanced hepatocellular carcinoma

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This study has been transitioned to CTIS with ID 2024-514049-13-01 check the CTIS register for the current data. to study the anti-tumor effect of cannabis oil (THC10% / CBD5%) in untreatable advanced HCC patients based on imaging using RECIST and…

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

Summary

ID

NL-OMON49322

Source
ToetsingOnline

Brief title
CanHep study

Condition

- Hepatobiliary neoplasms malignant and unspecified
- Hepatobiliary neoplasms malignant and unspecified

Synonym
hepatocellular carcinoma (liver cancer)

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Bedrocan International B.V.,PPP allowance

Intervention

Keyword: hepatocellular carcinoma, medicinal cannabis

Outcome measures

Primary outcome

Primary Endpoint:

to study objective response rate (ORR) of cannabis oil (THC10% / CBD5%) in

untreatable advanced HCC patients by assessing RECIST[14] and mRECIST [15]

criteria 6 months after starting cannabis oil.

Secondary outcome

Secondary Endpoint(s):

a. to study objective response rate of cannabis oil in untreatable advanced HCC

patients by assessing

- RECIST[14] and mRECIST[15] criteria at 3 and 9 months after starting cannabis

oil.

- levels of the tumor markers alfa-fetoprotein (AFP) and

des-gamma-carboxy-prothrombin (DCP) at 3, 6 and 9 months

b. to study quality of life at baseline, 3, 6 and 9 months using questionnaires

EORTC-QLQ C30 and EORTC- QLQ HCC18

c. to compare cannabinoid receptor expression in the tumor (based on histology)

between baseline and 6 months after treatment with cannabis oil.

d. to compare immune cell presence (including T-cells) in:

- blood at time points baseline, 3, 6 and 9 months after treatment with

cannabis oil. *

- tumor tissue at time points baseline and 6 months after treatment with

cannabis oil

*

Study description

Background summary

The incidence of hepatocellular carcinoma (HCC) has increased dramatically over the past decades. It appears frequently in patients with chronic liver disease, both in the presence or absence of cirrhosis. The development of HCC in cirrhotic liver is a multistep process that involves sustained inflammatory damage, including hepatocyte necrosis and regeneration, associated with fibrotic deposition in the liver. Additionally, HCC can also develop in non-cirrhotic liver. Although the mechanism of hepatocarcinogenesis in non-cirrhotic livers is not clear yet, important risk factors include non-alcoholic fatty liver disease (currently metabolic-associated fatty liver disease). The majority of patients present with hepatocellular carcinoma (HCC) at an advanced stage of cancer. It has been demonstrated that approximately one third of patients presenting with HCC were not suitable for any treatment and were offered best supportive care.

The biological activities attributed to cannabis are mainly been linked to the cannabinoids delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). These cannabinoids act on their receptors (cannabinoid-binding (CB) receptors). CB1 receptors mediate the behavioral and psychotropic effects of cannabinoids. By contrast, the cannabinoid receptor type 2 (CB2) is almost exclusively expressed by tissue of the immune system, including immune cells (lymphocytes and macrophages) and tissue (spleen, tonsils, lymph nodes). Here, they influence the release of cytokines and chemokines and migration of immune cells. The most well-known effect is caused by THC. It is the primary source of the psychoactive side effects of cannabis. THC is a partial agonist at CB1 and CB2

receptors with preferential binding to CB1. THC has well documented analgesic and anti-inflammatory benefits in arthritic and inflammatory conditions. It is 20 times more anti-inflammatory than aspirin, and twice as anti-inflammatory as hydrocortisone. CBD has much lower affinity for CB1 and CB2 receptors as compared to THC and it acts as a noncompetitive CB1 and CB2 receptor antagonist. This activity underlies its neutralizing actions on THC side effects such as anxiety, tachycardia, and sedation.

Anti-tumor effects of cannabinoids have also been described; results emerging from preclinical studies suggest that both THC and CBD elicit effects at different levels of cancer progression, including inhibition of proliferation, neovascularization, invasion and chemoresistance, induction of apoptosis and autophagy as well as enhancement of tumour immune surveillance. In case of hepatocellular carcinoma, THC has been demonstrated to reduce tumor growth both in vitro and in vivo via apoptosis induction. Interestingly, it appears that cannabinoid receptors have opposite roles. CB1 agonism appears to drive hepatocarcinogenesis through increased hepatocyte proliferation and liver fibrosis, where CB2 receptor reduce HCC formation and outgrowth by an anti-tumor immune response and induction of apoptosis.
Despite these preclinical results, clinical studies on the anti-tumor effect of cannabinoids are still lacking. Instead, many oncologic patient use cannabis oil for pain relief, reduction of chemotherapy-induced nausea and vomiting or appetite stimulation. It seems that many patients use cannabis oil without supervision, since cannabis oil can be bought on line. However, the exact concentrations of cannabinoids in the oils are unclear.

Recently, two of our patients demonstrated complete HCC tumor remission after being diagnosed (histologically proven) as untreatable. The first used cannabis oil (THC/CBD) every day. One year later, tumor size reduction was established by MR imaging. In 2017, total remission was observed after continuing cannabis oil. Until now, no recurrence has been diagnosed (last MRI 20-5-2020). A second patient was recently discovered with untreatable HCC who used cannabis oil (THC/CBD) after his initital diagnosis. He demonstrated reduction in tumor size and tumor markers during his follow up at the outpatient clinic. His last imaging did not demonstrate any active tumor tissue, but only rest necrosis. (last CT 23-9-2020).

Study objective

This study has been transitioned to CTIS with ID 2024-514049-13-01 check the CTIS register for the current data.

to study the anti-tumor effect of cannabis oil (THC10% / CBD5%) in untreatable advanced HCC patients based on imaging using RECIST and modified RECIST (mRECIST) criteria

Study design

This study will be a phase 2a study comprising 20 untreatable advanced HCC patients: 10 cirrhotic HCC patients (Child-Pugh A) and 10 non-cirrhotic HCC patients. Non-cirrhosis will be defined as normal livers and livers with stage F1 or F2 fibrosis based on METAVIR score

In case a patient has no exclusion criteria and when informed consent has been signed, an ultrasound- or CT guided biopsy will be performed for histological assessment of the tumor. If histology confirms HCC, patients will be included in the study and baseline parameters will be assessed. These include:
- Abdominal and thoracic CT (if not yet performed)
- blood analysis (37mL in total) for
o liver and kidney function, hematology, chemical blood profile
o tumormarkers (AFP and DCP)
o THC and CBD metabolites
o immune cells including T-cells
- Quality of life questionnaires

The presence of cirrhosis (or grading of fibrosis) will be determined on histology. In case insufficient liver tissue is present in the biopsy, presence of fibrosis or cirrhosis will be determined on imaging.

After inclusion, patients will be supplied with cannabis oil (Transvamix oil (THC10% / CBD5%)) provided by Felix Farma, distributed by the Transvaal Pharmacy. Every person reacts differently to cannabinoids due to a variety of reasons including different body compositions, liver function and underlying cannabinoid tone. Patients will be provided a titration scheme and self-titrate to their optimal daily dose. Optimal daily dose will be the maximum daily dose which does not produce adverse events. During the drug titration period (see chapter 6.6), we will have contact by telephone with patients every 2-3 days to determine the effective dose. After this, they will continue using this dose throughout the study. Patients will keep a daily log in which they note the dose (amount of droplets). Patients are free to skip a dose or reduce a dose because of side effects, they will note the reason for this in their daily log as well. The side effects are categorized as follows [in Dutch]:

1. Feeling high (a cheerful mood that slowly turns into a satisfied feeling of calm and tranquility)
2. Lethargy
3. Hunger
4. More intense experience of colors and /or sounds
5. Loss of sense of time and /or place
6. Gloomy and/or anxious mood
7. Restlessness and/or insomnia

8. Delusions
9. Increased heartrate
10. Dizziness
11. Hot or cold feeling in the hands and feet
12. Red burning eyes
13. Muscle relaxation
14. Dry mouth
15. Otherwise, namely*..

Every 3 months, tumor parameter assessment will be performed using:
- Abdominal and thoracic CT
- blood analysis (37mL in total) for
o liver and kidney function, hematology, chemical blood profile
o tumormarkers (AFP and DCP)
o THC and CBD metabolites
o immune cells including T-cells
- Quality of life questionnaires

At 6 months after starting cannabis oil, tumor biopsy will be repeated.

Intervention

Medical cannabis oil: Transvamix oil containing 10% tetrahydrocannabinol (THC) and 5% cannabidiol (CBD).

Study burden and risks

Patients who will participate should fullfill a titration period to determine the optimal daily dose of medicinal cannabis oil. For this, they will have contact every 2-3 days with a research nurse. After this they will use a daily log to note daily doses. Uing cannabis oil, patients are not allowed to drive a car until 2 weeks after the titration period (max. 7 weeks). Patients will visit the hospital three times for imaging purposes and outpatient clinic visits, including blood examination. Additionally, they will fill in quality of life questionnaires 3 times.
A possible benefit by anti-tumor effect is the subject of the study. Since HCC arising from cirrhotic livers may be different when arising from non-cirrhotic livers, both groups of patients will participate in this study.
The risk for this study is estimated to be low, according to the NFU risk classification. Of note, many oncological patients use cannabis oil without supervision.

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

- Age =>18 yrs
- Histologically proven hepatocellular carcinoma
- Non-cirrhosis or Child-Pugh A cirrhosis
- Hepatic encephalopathy grade 0 or 1
- MDT-advised best supportive care for untreatable advanced HCC or patients unable to undergo or declining treatment for advanced HCC.
- Minimal life expectancy of 3 months
- Willing and able to attend follow-up examinations
- Willing to stop active traffic participation or controlling machinery during the study period, when applicable
- Signed informed consent
- Language: Dutch or English

Exclusion criteria

- Mental conditions rendering the subject incapable to understand the nature, scope and consequences of the trial
- Use of medicinal cannabis for other purposes
- Child-Pugh B or C cirrhosis
- Hepatic encephalopathy grade 2 or more
- Previous systemic treatment for HCC
- Contra-indications for medicinal cannabis oil:
o Patients who have experienced a myocardial infarction or clinically significant cardiac dysfunction within the last 12 months or have had a cardiac disorder that, in the opinion of the investigator would have put the participant at risk of a clinically significant arrhythmia or myocardial infarction.
o Patients with known psychotic disorders
o Female patients who are pregnant or lactating
o Patients (men or women) intending to start a family
o Hypersensitivity to cannabinoids or any of the excipients of the cannabis oil

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-05-2021
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Transvamix
Generic name:	THC10% / CBD 5%

Ethics review

Approved WMO Date:	22-10-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-02-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-05-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-09-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-08-2024
Application type:	Amendment
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

ID: 28248

Source: Nationaal Trial Register
Title:

In other registers

Register	ID
Other	2018-004505-34
EU-CTR	CTIS2024-514049-13-01
EU-CTR	CTIS2024-514049-13-02
EudraCT	EUCTR2018-004505-34-NL
CCMO	NL68353.042.20