Pilot-study: Investigation of the safety of irreversible electroporation (IRE) as novel treatment for colorectal liver metastases - a phase I clinical study

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The primary objective of this study is to evaluate the safety in terms of complication rate of IRE in the treatment of colorectal liver metastasis/es

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

Summary

ID

NL-OMON37255

Source
ToetsingOnline

Brief title
Pilot study: Safety of Irreversible Electroporation (IRE) in CRLM

Condition

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

Synonym
Colorectal liver metastases, synonyme: metastases in the liver derived from colorectal carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Colorectal liver metastases (CRLM), Irreversible electroporation (IRE), NanoKnife, Tumor ablation

Outcome measures

Primary outcome

Primary outcome is the safety of the IRE procedure using the NanoKnife.

Secondary outcome

Secondary outcomes are feasibility (including procedure time), size and shape

of ablated area and the extent of cellular damage and apoptosis.

Study description

Background summary

Colorectal carcinoma is one of the most common malignancies in the Western world. 40-60% of the patients develop liver metastases in the course of the disease. Surgical resection is still the treatment of choice, but unfortunately up to 70% of the patients are not eligible for this treatment (1-3). Selected patients are offered thermal ablation therapy, such as RFA and microwave ablation. In recent years, SBRT has also emerged as a promising alternative. However, all these treatment modalities have their own shortcomings and the search for new local treatment techniques is ongoing.
Irreversible electroporation (IRE) is an ablation technique that takes advantage of the electric potential gradient that exists across cell membranes. The application of an electric field across a cell alters the transmembrane potential. On reaching a specific voltage, the bilayer structure of the cell membrane is permanently disrupted, inducing apoptosis. Recent findings resulting from animal studies using IRE on normal tissue show a sharply demarcated treatment area, with preservation of the - acellular - connective tissue architecture and major blood vessels in the ablated area. This is in contrast to thermal ablation techniques, where denaturation of proteins causes disruption of the connective tissue, destroying the anatomical framework. Being

non-thermal, the technique may not be susceptible to non-uniform ablation zones due to the 'heat-sink' effect (where tumor cells adjacent to a large vessel are prevented from adequate heating due to flowing blood carrying away the heat) as occurs with RFA, HIFU or microwave. In addition, IRE has demonstrated the potential for real-time monitoring with ultrasonography (US).
With these distinctive characteristics, IRE has the potential to become a successful alternative ablatoin method for solid tumors, especially in areas around large blood-vessels and vulnerable structures such as bile ducts, ureters or nerves.

Study objective

The primary objective of this study is to evaluate the safety in terms of complication rate of IRE in the treatment of colorectal liver metastasis/es <3,5 cm in patients undergoing surgical resection (metastatectomy, segmental liver resection or (extended) hemi-hepatectomy).

Study design

Single center pilot study

Intervention

Guideline indication for resectability of colorectal liver metastasis will be judged in consensus by a multidisciplinary liver team. After study inclusion, all patients will undergo a laparotomy according to the judgment of the surgeon. After liver exposure the interventional radiologist will position the probes under ultrasound guidance and will start ablation with the NanoKnife according to protocol under careful ECG monitoring. After ablation, the surgeon will proceed with the resection of the metastasis. Standard histological examination of the specimen, with additional caspase-3 analysis will be performed.

Study burden and risks

Participation in the study will not cause a significant additional burden for the patient.

Participation in the study will probably not be associated with additional risks for the patient. However, the goal of this study is to prove the safety of IRE and therefore this needs to be confirmed by means of this study. Preclinical as well as clinical studies show a favorable complication profile in comparison to other local treatment modalities in the liver, due to the non-thermal treatment effect. IRE carries a small risk of bleeding, fistula formation or infection that is comparable to other procedures were needles are inserted into the body, especially when 2 or 3 needles are used at once.

Additionally, due to the high voltage used with IRE, there is a small risk of precipitating muscle contractions, bradycardia/hypotension and cardiac arrhythmias. However, since the use of the Accusync ECG gating device, which enables synchronized pulsing, no irregularities have been observed within the registry (now including >1000 patients). Muscle contractions will be prevented/treated with additional muscle relaxants during the procedure. Rare complications of IRE additional to liver surgery are electric shock, myocardial infarction, CVA and vagal stimulation .

Participation in the study will not lead to an individual benefit for the patient, but participation might contribute to the development of better future treatment strategies in solid tumors.

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

Screening must be performed no longer than 4 weeks prior to study inclusion. Subjects are eligible if they meet the following criteria:
* Histological or cytological documentation of primary colorectal tumor
* Liver metastases visible on FDG PET-CT or contrast-enhanced CT, size * 3,5 cm.
* Resectability (re)confirmed by intraoperative US
* Age 18 years or older
* WHO performance status 0 * 2
* Life expectancy of at least 12 weeks
* Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to definite inclusion:
Hemoglobin * 5.6 mmol/L; Absolute neutrophil count (ANC) * 1,500/mm3; Platelet count * 100*109/l; Total bilirubin * 1.5 times the upper limit of normal (ULN); ALT and AST * 2.5 x ULN; Serum creatinine * 1.5 x ULN or a calculated creatinine clearance ³ 50 ml/min; Prothrombin time or INR < 1.5 x ULN;
Activated partial thromboplastin time < 1.25 x ULN (therapeutic anticoagulation therapy is allowed if this treatment can be interrupted as judged by the treating physician).
* Written informed consent.

Exclusion criteria

Subjects who meet the following criteria at the time of screening will be excluded:
* Lesion > 3,5 cm
* History of cardiac disease:
- Congestive heart failure >NYHA class 2;
- Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening);
- Cardiac arrhythmias requiring anti-arrhythmic therapy or pacemaker (beta blockers are permitted)
* History of epilepsy
* Uncontrolled hypertension. Blood pressure must be *160/95 mmHg at the time of screening without medication or on a stable antihypertensive regimen.
* Uncontrolled infections (> grade 2 NCI-CTC version 3.0).
* Pregnant or breast-feeding subjects. Women of childbearing potential must have a negative pregnancy test performed within 7 days of the start of treatment.
* Immunotherapy * 6 weeks prior to the procedure
* Chemotherapy within 12 weeks before surgery
* Radiotherapy, RFA or MWT treatment of target lesions prior to resection
* Concomitant use of dexamethasone, anti-convulsants and anti-arrhythmic drugs.
* Severe allergy for contrast media not controlled with premedication.
* Any condition that is unstable or could jeopardize the safety of the subject and their compliance in the study.

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):	02-11-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Peroperative irreversible electroporation (radiological intervention)
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	18-09-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

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
CCMO	NL41089.029.12