COLDFIRE-2 study: Colorectal metastatic liver disease: efficacy of irreversible electroporation (IRE) - a phase II clinical trial

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The primary objective of this project is to evaluate the primary and secondary technique effectiveness of IRE for centrally located colorectal liver metastases that are neither amenable for resection nor for other local ablation methods due to the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44806

Source
ToetsingOnline

Brief title
COLDFIRE-2: efficacy of IRE for colorectal liver metastases

Condition

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

Synonym
Colorectal liver metastases, synonyme; metastasesin the liver derived from colorectal carcinoma

Health condition

colorectale levermetastasen

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

The primary endpoint is efficacy of IRE as expressed in primary technique effectiveness (by perfoming imaging after 3, 6, 9 and 12 months) also expressed by the local IRE site recurrence (LSR) on a per-lesion basis, and secondary technique effectiveness on a per-lesion basis after repeat procedures for local recurrences whenever indicated.

Secondary outcome

Secondary endpoints are (1) safety, derived from number and grade of (serious) adverse events using the common terminology reporting criteria (CTCAE version 3.0) as recommended by the CIRSE quality approvement guidelines, (2) technical success, defined as the ability to successfully administer all pulses and to have complete tumor coverage on immediate post-IRE imaging (by IOUS or CT) (3) feasibility of cross-sectional imaging modalities to detect local recurrences after IRE, and (4) symptomatic response using specific quality of life questionnaires.

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 resection. Selected patients are offered other local treatment modalities like radiofrequency ablation (RFA), microwave ablation and stereotactic ablative radiation therapy (SABR). A shortcoming of these modalities is that they are not suitable for lesions close to large vessels and/or bile ducts: the heat can destruct the bile ducts, leading to biliary complications and the vicinity of large vessels can lead to inadequate heating due to *heat-sink* (where tumor cells adjacent to a large vessel are prevented from adequate heating due to flowing blood carrying away the heat), which causes a higher percentage of local recurrences. Therefore, the search for new local treatment therapies 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 sufficiently high voltage, the phospholipid 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. IRE relies on electrical energy, not thermal energy, for achievement of cell death and appears to be unaffected by heat-sink. This suggests a potentially more effective treatment of an area with tumor cells in close proximity to large vessels, such as centrally located liver lesions. In addition, IRE has demonstrated the potential for real-time monitoring with ultrasonography (US). Electroporation leaves supporting tissue largely unaffected so the structure of large blood vessels, bile ducts, ureters and nerves is preserved.
With these distinctive characteristics, IRE has the potential to become a successful alternative ablation method for solid tumors, especially in areas around large blood vessels and vulnerable structures such as centrally located colorectal liver metastases (CRLM) that are not amenable for resection or thermal ablation.

Study objective

The primary objective of this project is to evaluate the primary and secondary technique effectiveness of IRE for centrally located colorectal liver

metastases that are neither amenable for resection nor for other local ablation methods due to the proximity of vital structures. Imaging will be performed respectively 2 weeks post-IRE and after 3, 6, 9 and 12 months Secondary objectives are safety, technical success and characterization of CT-, MRI, PET-CT and PET-MRI findings after IRE to determine the utility of these findings in the accurate assessment of the ablation zone and early detection of local site recurrence.
Study design: Multi-center combined phase I/II cohort study.

Study design

Multi-center phase II cohort study.

Intervention

Patients with CRLM who are considered candidates for local therapy, based on their tumor load, medical history and general health status, but who are not suitable for resection or thermal ablation due to the anatomical location of at least one of the lesions, will be included after careful judgment in consensus by our multidisciplinary liver team. Limited extrahepatic disease is not a contra-indication whenever these lesions can be treated as well, during or within 4 weeks after the IRE procedure. After study inclusion, patients will undergo percutaneous or open IRE. Percutaneous procedures are performed under CT-guidance with or without ultrasound (US) guidance. Open procedures are performed with intra-operative ultrasound (IOUS). After correct placement of the electrodes IRE will be performed under ECG monitoring (70 pulses; pulse length 90µs per pulse; 1200-1500V/cm; 20-50Ampere; electrode distance 1.5-2.5 cm; active working length 2.0cm) between all electrode pairs (NanoKnife, Angiodynamics, Latham, NY, USA). After the IRE procedure, additional CRLM can be resected or treated with RFA or MWA within the same session. Follow-up will be with PET-CT (including ceCT) (and PET-MRI including ceMRI in VUmc only).

Study burden and risks

Preclinical as well as clinical studies show a low complication profile in comparison to other local treatment modalities in the liver. Because of the high voltage used with IRE, the procedure carries a small risk of inducing cardiac arrhythmias, although since the use of the Accusync ECG gating device, which enables synchronized pulsing, no clinically significant arrhythmias have been observed within the registry (now including >1400 patients including at least 30 patients treated in our institution so far for heterogeneous salvage indications such as participation in our COLDFIRE-1 ablate and resect study for resectable CRLM). Because of the non-thermal treatment effect IRE is presumably a safer option causing less collateral damage to adjacent or inlaying vital structures. The NanoKnife IRE system is CE marked and FDA approved for image-guided ablation of soft tissue in humans. Patients who agree to

participate in the study will undergo IRE of liver lesions not considered treatable by resection or thermal ablation. They will undergo follow-up PET-CT (including ceCT) (and PET-MRI including ceMRI in VUmc) performed on the same day at 6 weeks, and after 3, 6, 9 and 12 months after IRE. Additionally PET-MRI is used to investigate its feasibility in the follow-up to detect local recurrences as compared to PET-CT and ceCT. In case of local site recurrence, patients will be re-treated whenever feasible with the most suitable therapy.

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;

• Previous induction chemotherapy due to unresectability; no intra- or extrahepatic disease progression under induction chemotherapy; OR
• Previous chemotherapy for other CRLM, now presenting with renewed CRLM unsuitable for resection or thermal ablation;
• Liver metastases F-18-FDG PET avid and visible on ceCT, size <= 3,5 cm and not eligible for resection or thermal ablation due to location close to a vessel or bile duct;
• Age >= 18 years;
• ASA classification 0 - 3;
• Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted within 7 days prior to definite inclusion:
o Hemoglobin >= 5.6 mmol/L;
o Absolute neutrophil count (ANC) >= 1,500/mm3;
o Platelet count >= 100*109/l;
o Total bilirubin <= 1.5 times the upper limit of normal (ULN);
o ALT and AST <= 2.5 x ULN
o Serum creatinine <= 1.5 x ULN or a calculated creatinine clearance * 50 ml/min;
o Prothrombin time or INR < 1.5 x ULN;
o 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 size;
• History of epilepsy;
• Extrahepatic metastases rendering local therapy unfeasible;
• History of cardiac disease:
o Congestive heart failure >NYHA class 2;
o Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening);
o Cardiac arrhythmias requiring anti-arrhythmic therapy or pacemaker/ICD (beta blockers are permitted);
• Uncontrolled hypertension. Blood pressure must be <=160/95 mmHg at the time of screening on a stable antihypertensive regimen;
• Compromised liver function (e.g. signs of portal hypertension, INR > 1,5 without use of anticoagulants, ascites);
• Pregnant or breast-feeding subjects;
• Immunotherapy <= 6 weeks prior to the procedure;
• Chemotherapy <= 6 weeks prior to the procedure;
• Use of anti-convulsives and anti-arrhythmic drugs other than beta blockers for antiepileptic or antiarrhythmic purpose;
• Allergy to contrast media which cannot be adequately prevented with the standard contrast allergy prevention regimen;
• Any condition that is unstable or that could jeopardize the safety of the subject and their

compliance in the study

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):	23-06-2014
Enrollment:	50
Type:	Actual

Medical products/devices used

Generic name:	Irreversible electroporation using the NanoKnife-system
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	16-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2017
Application type:	Amendment
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	NL47818.029.14