PANFIRE - Pilot-study: Non-thermal ablation using Irreversible Electroporation (IRE) to treat locally advanced pancreatic carcinoma - a phase I clinical study

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In this pilot-study we investigate the safety, feasibility and efficacy of IRE in locally advanced pancreatic carcinoma. We hypothesize that IRE of the pancreas is a safe treatment that will cause few complications. Moreover, we expect the treatment...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Exocrine pancreas conditions
Study type	Interventional

Summary

ID

NL-OMON41424

Source
ToetsingOnline

Brief title
Pilot-study: Treatment of LAPC with Irreversible Electroporation (IRE)

Condition

- Exocrine pancreas conditions
- Appetite and general nutritional disorders
- Gastrointestinal neoplasms malignant and unspecified

Synonym
locally advanced pancreatic carcinoma, synonyme: inoperable pancreatic cancer without metastases

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: Irreversible Electroporation (IRE), Locally advanced pancreatic carcinoma (LAPC), NanoKnife, Tumor ablation

Outcome measures

Primary outcome

Primary outcome of the study is the safety of IRE for the treatment of locally advanced pancreatic carcinoma, By registration and analysis of adverse events and serious adverse events, incidence and severity of complications within 90 days after the intervention are investigated and morbidity and mortality will be determined. Late complications that might be related to the intervention (listed in the study protocol under paragraph 12.1), will always be registered and reported if necessary (in case of SAE's). These results will be compared to patients that have undergone radio- and or chemotherapy alone.

Secondary outcome

Secondary parameters are (see paragraph 2.1.2. from the project protocol):

- Feasibility: parameters are willingness of patients to participate, number of eligible patients, total procedure time, ablation time, number of tme of replacement of the electrodes (expressed in learning curve)

-Efficacy, as expressed in:

1. Symptomatic response: Quality of life, pain registration and pain medication

and general performance status

2. Tumor evaluation: Size and shape of the ablation area, ablation success and

local recurrence rate (by CT and MRI)

- Immunologic response: by investigating the T-cell specific immune reaction,

before, 2 weeks and 3 months after IRE.

- Exocrine pancreatic function, smaal bowel absorption capacity and body fat

composition

Study description

Background summary

Cancer of the exocrine pancreas is the fourth leading cause of cancer-related death in Western-Europe and the US and is second only to colorectal cancer as a cause of digestive cancer-related death. The majority of these tumors (85 percent) are adenocarcinomas arising from the ductal epithelium.
Surgical resection is the only potentially curative treatment. Unfortunately, because of the generally late presentation of the disease, only 15 to 20 percent of patients are candidates for operation with curative intent. Forty percent of patients have locally advanced pancreatic carcinoma (LAPC) at the time of diagnosis and another forty percent have concurrent metastatic disease. The prognosis of pancreatic cancer is poor, even in those resected with curative intent. The median survival after resection for pancreatic adenocarcinoma is only 12.6 months, with a five-year survival of 3 to 31 percent (stage IA, 31.4%; IB, 27.2%; IIA, 15.7%; IIB, 7.7%; III, 6.8%; IV, 2.8%). In these patients, tumor size, nodal status and distant metastases all affect the likelihood of death.
The primary goals of treatment for LAPC are palliation of intractable pain and obstruction and improved overall survival. Observational and phase II studies of patients with borderline and locally advanced tumors suggest a *downstaging

effect* of chemotherapy, with main agents gemcitabine, 5-FU, and cisplatinum, in some rare cases allowing future resection. For patients with locally advanced, nonmetastatic disease (typically a T4 lesion) and patients with metastatic disease, chemoradiation (with gemcitabine or 5-fluorouracil (5-FU)) has proven to prolong survival and to improve quality of life (QoL). However, median survival remains extremely poor at 6 to 11 months.
In the past years, non-surgical local treatment therapies for tumors in different organs have broadly developed, such as cryoablation, and heat-mediated ablation methods such as radiofrequency ablation (RFA), high intensity focused ultrasound (HIFU), laser-ablation and microwave ablation (MWA). These ablative therapies have also been studied in patients with LAPC to achieve better palliation through cytoreduction. However, the use of thermal tumor ablative techniques in the pancreas is limited due to the high risks involved. Denaturation of proteins due to the heat causes disruption of connective tissue and destroys the anatomical framework, leading to pancreatitis and damaging major vascular structures in LAPC. A complete ablation in LAPC is therefore not realistic.The so called *heat-sink* effect, in which tumor cells adjacent to a large vessel are prevented from adequate heating due to flowing blood, which cools adjacent tissue can lead to incomplete ablation. This effect is another drawback in the performance of RFA in LAPC, since the tumor is surrounded typically by major vessels.
Therefore, the search for new local ablative methods is ongoing, particularly for pancreatic cancer. 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. Also, since IRE relies on electrical energy, and not on thermal energy, its effectiveness appears to be unaffected by the *heat-sink* effect. This suggests a potentially more effective treatment of an area with tumor cells in close proximity to large vessels. Moreover, there are indications that IRE induces a cellular immune response in the lymph nodes draining the area of ablation. If this immune reaction can be harnessed, it could result in the destruction of micro-metastases in the affected lymph nodes which could affect survival. In addition, the procedure time will be much shorter compared to thermal ablation methods and surgical resection.
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 the pancreas. Early clinical data on IRE in the pancreas for treatment of pancreatic carcinoma are promising, with good local palliation and local control and even improved overall survival.
To investigate the safety, feasibility and efficacy of IRE in the treatment of

LAPC, we designed a pilot study. We hypothesize that IRE in the pancreas will induce good symptom palliation and local control.

Study objective

In this pilot-study we investigate the safety, feasibility and efficacy of IRE in locally advanced pancreatic carcinoma. We hypothesize that IRE of the pancreas is a safe treatment that will cause few complications. Moreover, we expect the treatment to lead to good local tumor control and better symptom palliation. This will hopefully lead to an improvement of quality of life.
Also, the immunologic response that is induced by IRE will be investigated. Furthermore, the influence of IRE on the exacrine pancreatic function and the small bowel absorption capacity is investigated, which is important to guide adequate adminitration of nutrition supplements and advice with respect to intake.

Study design

Multi center pilot study

Intervention

Criteria for LAPC are based on the guidelines of the National Comprehensive Cancer Network. For each individual patient, these criteria will be judged in consensus by a multidisciplinary hepatobiliary team. A contrast enhanced computed tomography scan (ceCT) of the chest and abdomen will be performed to exclude metastatic disease. Baseline tumor marker CA 19-9 will be measured. To investigate the cellular immune response, baseline mesothelin will be measured and cultured in vitro, after which T-cell response will be examined. Quality of life questionnaires will be filled in. A day before the procedure, pancreatic MRI will be performed. Percutaneous IRE will be performed under CT-guidance. After satisfactory electrode placement, tumor ablation with the NanoKnife will be performed according to protocol under careful ECG-monitoring. Also, during the procedure, possible epileptic activity will be recorded by EEG-registration. Postprocedurally, pancreatic and hepatic enzymes will be monitored. One day after the procedure, pancreatic MRI will be performed to investigate the imaging after the procedure. Two weeks later, mesothelin will be measured again to compare the immune response to mesothelin to baseline. Follow-up will consist of regular assessment of performance status by the physician, ceCT- and MRI -scanning and serum marker CA 19.9. To assess the effect of the treatment on the quality of life, questionnaires will be filled in. Furthermore, before and after the procedure, the exocrine pancreatic function and smaal bowel absorption capacity is investigated by means of fecal sampling and blood sampling, and the resting metabolism and body fat percentage are measured.

Study burden and risks

Preclinical as well as clinical studies using IRE show a favorable complication profile for local tumor treatment in comparison to other local treatment modalities in distinct cases. IRE is a potentially useful technique to treat tumors near vital structures, as is the case in pancreatic cancer. However, the number of treated patients is still relatively small. Therefore, more prospective studies are needed to evaluate the safety, feasibility, effectiveness and potential benefits of this technique.
Patients with LAPC are confronted with a grave prognosis with a short life expectancy and severe complications to be expected due to local tumor ingrowth and metastatic disease. Treatment with the NanoKnife might be the only potentially successful treatment with respect to local symptom palliation and to achieve local tumor control. The first reports of patients with LAPC treated with IRE are promising. In one study in which open IRE was performed on 54 patients, the results were compared to a control group that received standard (radio)chemotherapy. The authors demonstrated that even in the patients who did not undergo IRE, after 4 months of induction therapy, there remains significant morbidity in those patients, which in some instances is as severe as in surgical patients, or even worse. The authors state that the rationale that patients with LAPC are spared surgical or interventional radiological therapy is unsubstained and should continue to be evaluated even after initial diagnosis.
In this study, we offer patients a potential method to prevent, delay and/or decrease the expected complications or their severity from happening. We hypothesize that treatment with the NanoKnife will lead to a drop in morbidity, by achieving tumor size reduction without the necessity of performing extensive surgery. Hopefully, tumor size reduction will decrease and delay pain and obstructive complaints. In conclusion, the participants will undergo a new and relatively experimental procedure that is regarded to be safe but carries a certain risk, but if our hypothesis will prove to be right participants will profit from better symptom palliation and have a better QoL and possibly better OS. From this perspective, we believe the additional risk of treatment with the NanoKnife is justified, for the best interest of the patient.

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 2 weeks prior to study inclusion. Subjects are eligible if they meet the following criteria:;* Histologic or cytologic confirmation of primary pancreatic carcinoma;
* Radiologic confirmation of unresectable pancreatic carcinoma without distant metastases by at least ceCT of chest and abdomen, performed maximum 2 weeks prior to the procedure;
* Maximum tumor diameter * 5 cm;
* Age * 18 years;
* ASA-classificaton 0 * 3;
* 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 bilirubine * 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 * 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:
* Resectable pancreatic adenocarcinoma as discussed by our multidisciplinary hepatobiliary team;
* Extrapancreatic metastases;
* Successful downstaging after (radio)chemotherapy from previous unresectable/borderline tumor to resectable tumor;
* History of epilepsy;
* History of cardiac disease:
- Congestive heart failure >NYHA class 2;
- Active Coronary Artery Disease (defined as myocardial infarction within 6 months prior to screening);
- Ventricular cardiac arrhythmias requiring anti-arrhythmic therapy or pacemaker (beta blockers for antihypertensive regimen 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);
* 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 * 6 weeks prior to the procedure;
* Radiotherapy * 6 weeks prior to the procedure;
* Concomitant use of anti-convulsive and anti-arrhythmic drugs (other than beta blockers for hypertension);
* Allergy to contrast media;
* Any implanted stimulation device;
* 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:	Recruiting
Start date (anticipated):	06-01-2014
Enrollment:	40
Type:	Actual

Medical products/devices used

Generic name:	Percutaneous irreversible electroporation (interventional radiology)
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	29-08-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2015
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	NL42888.029.13