Trial Description

Title

Pancreatic resection with perioperative off-Label study of Propranolol and Etodolac - A Phase II randomized Trial

Trial Acronym

PROSPER

URL of the trial

[---]*

Brief Summary in Lay Language

Pancreatic cancer is a severe disease, which is often diagnosed at an advanced stage. Therefore, only few patients can be healed by a combination of surgery and chemotherapy (either before or after surgery). However, chemotherapy has to be suspended for a certain time before, during and after surgery in order not to increase surgical risk. The combination therapy of propranolol, a beta-blocker that is usually used to treat arterial hypertension or cardiac arrhythmia, and etodolac, an antiinflammatory pain medication, have indicated in former studies that physical and psychological stress responses related to surgery may be reduced. This might have a positive impact on the course of the disease and the oncologic prognosis.
Therefore, this combination therapy will be tested and compared to a placebo (dummy drug). Patients and doctors will be blinded to the treatment (that means they will not know who is taking which drug). The main objective of the study will be to evaluate safety and feasibility of the combination therapy and to create first data on efficacy for planning of a subsequent larger trial. All adult patients scheduled for elective resection of the pancreatic head due to cancer may participate in the trial unless they fulfill any of the exclusion criteria (substantial comorbidities, allergies or contraindications for the study medication etc.).

Brief Summary in Scientific Language

Pancreatic cancer has a poor prognosis and its incidence is rising in recent years. The majority of pancreatic cancer patients present with locally advanced or metastatic disease and only a minority of patients is treatable in curative intent usually by a combination of surgery and chemotherapy. However, chemotherapy has to be suspended during the perioperative period in order not to increase surgical morbidity.
The perioperative period represents a window for cancer directed treatment that is currently unexploited. Combination therapy of propranolol and etodolac in the perioperative setting promises an effective attenuation of tumor-associated inflammation by inhibiting psychological, surgical and inflammatory stress responses. By these mechanisms, relevant antitumorigenic and antimetastatic effects may possibly be achieved during the perioperative period.

The primary objective of this 2-arm randomised, patient and observer blinded, placebo-controlled, phase-2 trial is to evaluate safety and feasibility of

perioperative propranolol and etodolac treatment in patients with resectable cancer of the pancreatic head planned for elective pancreatoduodenectomy.

Do you plan to share individual participant data with other researchers?

Yes

Description IPD sharing plan

A full deidentified individual patient dataset of the trial will be made available after trial completion and publication upon reasonable request from the principal investigator.

Organizational Data

- DRKS-ID: **DRKS00014054**
- Date of Registration in DRKS: **2018/08/29**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **AFmo-385/2018 , Ethik-Kommission I der Medizinischen Fakultät Heidelberg**

Secondary IDs

- EudraCT-No.
  (for studies acc. to Drug Law): **2018-000415-25**

Health condition or Problem studied

- ICD10: **C25.0 - Malignant neoplasm: Head of pancreas**

Interventions/Observational Groups

- Arm 1: **Propranolol 2x20 mg/day, p. o.: 10 days before surgery; Propranolol 2x40 mg/day, p.o.: day of surgical intervention and 1st day until 7th day after operation; Propranolol 2x20 mg/day, p. o.: 8th until 14th day postoperative. Etodolac 2x400 mg/day p. o., 10 days before surgery until 14th day postoperative**
- Arm 2: **Placebo with similar shape compared to Propranolol 2x1/day, p. o.: 10 days before surgical intervention; 2x2/day p.o.: Day of Operation, and 1st to 7th day postoperative;**
  2x1/day, p. o.: 8th to 14th day postoperative.
  Placebo with similar shape compared to Etodolac 2x1/day p. o., 10 days before operation until 14th day postoperative.

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **patient/subject, investigator/therapist, caregiver, assessor**
- Control: **Placebo**
- Purpose: **Treatment**
- Assignment: **Parallel**
- Phase: **II**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **Yes**

Primary Outcome

Safety endpoints:
•Rates of serious adverse events and serious adverse drug re-actions
•Mortality at 30 and 90 days postoperatively
•Pancreas-associated morbidity (Pancreatic fistula, delayed gas-tric emptying, postoperative pancreatic hemorrhage, biliary leakage, fluid collection/abscess)

Feasibility endpoints:
•Adherence to study medication
•Completion of adjuvant chemotherapy

Secondary Outcome

Oncologic endpoints:
•Overall survival
•Disease-free survival
•Rates of local / distant recurrence

Biological endpoints/Biomarkers (will be measured at different timepoints of study conduct):
•Blood samples: c-reactive protein (CRP), albumin, differential blood count, CA 19-9, carcinoembryonic antigen (CEA), cyto-kine multiplex, PGE-2 levels, circulating tumor cells, RNA se-quencing in periphery blood cells (leukocytes)
•Tissue samples: COX-2 expression, PGE-2 levels, immune cell infiltrate (immunehistochemistry), RNA sequencing of bulk tis-sue or of sorted tumor and stromal cells

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Klinik für Allgemein-, Viszeral- und Transplantationschirurgie, Heidelberg**

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2019/01/23**
- Target Sample Size: **100**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

•Resectable malignancy of the pancreatic head, eligible for elective pancreatoduodenectomy in curative intent
•WHO / ECOG performance status 0-2
•Age ≥ 18 years
•ASA score I-III
•Patient must be able to understand the consequences of trial participation and to provide written informed consent
•Written informed consent from the trial subject has been obtained
•Female subject must be postmenopausal (for at least 6 months), surgically sterile, abstinent, or, if sexually active, be practicing an effective method of birth control (e.g., prescription of oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; and have a negative serum ß-hCG pregnancy test at screening

Exclusion criteria

•Any contraindication for pancreatoduodenectomy
•Metastatic disease (Stage IV)
•Patients scheduled for palliative resection (no curative treatment intention)
•Patients scheduled for extended resections (arterial resections, planned multivisceral resections)
•Preoperative CA 19-9 > 400 U/ml
•Acute or ongoing episode of cholangitis (fever and pain in the right upper quadrant of the abdomen together with increased infectious parameters and elevated AP & GGT values)
•Acute or ongoing episode of pancreatitis (clinical symptoms of pancreatitis, increased lipase and/or CRP values, radiological or intraoperative signs of acute pancreatitis)
•Chronic neuropathy > grade 2
•Renal failure, measured by GFR <50ml/min/1,73 m² (calculated according to CKD-EPI)
•Known liver cirrhosis of any grade
•Atrioventricular block

•Previous neoadjuvant chemotherapy
•Pregnant or breastfeeding women
•Mental or organic disorders which could interfere with giving informed consent or receiving treatments
•Any contraindication to propranolol and/or etodolac:
-Known allergy or hypersensitivity to propranolol and/or etodolac or any other ingredient of the used brand
-History or evidence of significant cardiac disease: congestive or severe heart failure; New York Heart Association class ≥ 2; active coronary artery disease; unstable angina, cardiac arrhythmias requiring anti-arrhythmic therapy, uncontrolled hypertension, patients with recent (less than 6 months) myocardial infarction or coronary revascularization; cardiogenic shock; sick sinus Syndrome; sinuatrial block; acidosis
-Hypotension at the time of screening (i.e., systolic blood pressure less than 100 mmHg. Diastolic blood pressure less than 60 mmHg)
-Symptomatic bradycardia or resting heart rate less than 50 bpm at time of Screening
-Bronchial hyperresponsiveness, including active chronic asthma
-Active peptic ulcer disease or gastrointestinal bleeding
-Decompensated diabetes mellitus (repeated measurements of glucose >300 mg/dl despite usual medical treatment, (keto-) acidosis, exsiccosis due to decompensated diabetes)
-Chronic inflammatory bowel disease (M. Crohn or Ulcerative colitis)
-Severe peripheral vascular disease
-Concurrent use of MAO inhibitor (excluding MAO-B inhibitor)
-Intravenous application of calcium channel blockers (Nondihydropyridine) and other antyarrhythmic agents
-Severe thrombocytopenia
-Sensitivity to Aspirin or other NSAIDs in Terms of athma, urticaria or acute rhinitis
-Chronic use of any beta-adrenergic blocker within the last 3 months.
-Chronic use of any COX inhibitor within the last 3 months.
-Participation in another interventional trial
-Pharmaceutical preparations with which major interactions can be expected by propranolol/etodolac in patients' long-term therapy
-Diseases or findings that may have a significant effect on the target variables and which may therefore mask or inhibit the therapeutic effect under investigation
-Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
-Persons held in an institution by legal or official order; legally incapacitated patients
-Persons with understanding/language problems or inability to comply with study and/or follow-up procedures
-Any condition which could result in an undue risk for the patient and/or influence out-come measures in the opinion of the investigator

Addresses

■ **Primary Sponsor**

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■ **Contact for Scientific Queries**

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■ **Contact for Public Queries**

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Sources of Monetary or Material Support

- **Private sponsorship (foundations, study societies, etc.)**

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  Boechoutlaan 221
  1853 Strombeek-Bever
  Belgium

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

- **Institutional budget, no external funding (budget of sponsor/PI)**

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  Im Neuenheimer Feld 110
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  URL: **[---]***

Status

- Recruitment Status: **Recruiting stopped after recruiting started**
- Reason, if "Recruitment stopped after recruiting started" or "Recruiting withdrawn before recruting started": **Ungenügende Rekrutierung**
- Reason, if Reason for Recruiting Stop "Other": **[---]***
- Study Closing (LPLV): **2021/07/09**
- Number of Participants in Germany after Recruiting complete: **26**
- Total Number of Participants (all Sites worldwide) after Recruiting complete: **26**

Trial Publications, Results and other documents

- trial protocol (mandatory for transfer to Studybox) **Publikation des Studienprotokolls**

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*