ISRCTN65518365 https://doi.org/10.1186/ISRCTN65518365

Uracil and ftorafur (UFT) and radiotherapy in patients with locally advanced pancreatic cancer

Submission date 31/08/2010	**Recruitment status** Stopped	[_] Prospectively registered [_] Protocol
Registration date 04/10/2010	**Overall study status** Stopped	[_] Statistical analysis plan [X] Results
Last Edited 04/03/2016	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
http://www.cancerhelp.org.uk/trials/a-study-new-treatment-plan-locally-advanced-cancer-pancreas-peru

Contact information

Type(s)
Scientific

Contact name
Dr Ian Chau

Contact details
The Royal Marsden NHS Foundaton Trust
Downs Road
Sutton
United Kingdom
SM2 5PT
-
ian.chau@rmh.nhs.uk

Additional identifiers

Protocol serial number
3065

Study information

Scientific Title

A multicentre randomised phase II clinical study of uracil and ftorafur (UFT) and radiotherapy with or without cetuximab following induction gemcitabine plus capecitabine in patients with locally advanced pancreatic cancer

Acronym
PERU

Study objectives
Locally advanced pancreatic cancer carries a poor prognosis. There has been no definite survival advantage of chemoradiotherapy (CRT) over chemotherapy alone. However, in a retrospective analysis of 4 phase II - III studies, patients without disease progression after 3 months of systemic chemotherapy and proceeded to CRT had a longer survival than those continuing on chemotherapy. In this selected subgroup of locally advanced pancreatic cancer patients, the strategy of systemic chemotherapy followed by CRT may be a better treatment approach. In this randomised phase II trial, this treatment approach will be evaluated in a prospective fashion and in addition, the effect of adding epidermal growth factor receptor (EGFR) blockade to CRT will be evaluated in locally advanced pancreatic cancer. Gemcitabine and capecitabine combination will be used as neo-adjuvant chemotherapy based on recent survival benefit shown over gemcitabine alone. UFT/LV will be used subsequently during CRT as it has very low incidence of skin reaction and hand foot syndrome, giving it the rationale to use after a prolonged period of capecitabine treatment and also in conjunction with cetuximab.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Leicestershire, Northamptonshire and Rutland Research Ethics Committee 1, 26/03/2009

Study design
Multicentre randomised phase II clinical study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Locally advanced pancreatic cancer

Interventions
1. Neoadjuvant gemcitabine and capecitabine:
1.1. Gemcitabine 100 mg/m2 intravenous (iv) infusion over 30 minutes, the lyophilised powder being diluted in normal saline. Administered on days 1, 8 and 15. Dose banding according to local practice is permitted
1.2. Capecitabine 830 mg/m2 twice daily (total daily dose of 1660 mg/m2) will be administered orally for 21 days followed by 7 days rest. Capecitabine tablets should be administered morning and evening and swallowed with water within 30 minutes of a meal.

2. Chemoradiation:
2.1. Arm A: uracil and ftorafur (UFT) plus radiotherapy -
2.1.1. UFT 300 mg/m2/day in 3 equal doses days 1 - 42 (on days of RT only; 30 days in total)
2.1.2. Leucovorin 90 mg/day in 3 divided doses days 1 - 42 (on days of RT only; 30 days in total)
2.1.3. Radiotherapy 54 Gy in 30 fractions over 6 weeks
2.2. Arm B: uracil and ftorafur (UFT) plus cetuximab plus radiotherapy -
2.2.1. Cetuximab 400 mg/m2 (first dose) day 1 then 250 mg/m2 (subsequent doses) iv once weekly for the following 5 weeks (total weekly dose x 6)
2.2.2. UFT 300 mg/m2/day in 3 divided doses days 1 - 42 (on days of RT only; 30 days in total)
2.2.3. Leucovorin 90 mg/day in 3 divided doses days 1 - 42 (on days of RT only; 30 days in total)
2.2.4. Radiotherapy 54 Gy in 30 fractions over 6 weeks

3. Post chemoradiation gemcitabine and capecitabine:
The same treatment schedule should be used as neo-adjuvant gemcitabine and capecitabine. Patients who have had dose reduction during neo-adjuvant GEM-CAP should commence with the reduced dose post-chemoradiation. GEM-CAP should be given for 2 further cycles, but can be given for as long as patient is deriving clinical benefit or until disease progression or intolerable toxicity.

4. Follow-up:
4.1. If a patient has completed neo-adjuvant chemotherapy, but has not undergone randomisation or chemoradiation, follow up arrangements will be left to the treating clinician's discretion. However, survival status should be ascertained at least once every 6 months.
4.2. For patients who have finished chemoradiation and adjuvant GEMCAP, first follow-up clinic visit with physical examination will be four weeks after chemotherapy for post-treatment CT results, thereafter three monthly during year 1, six monthly during the years 2 and 3 and then annually for years 4 and 5.
4.3. For patients not receiving post-chemoradiation GEM-CAP chemotherapy, first follow up clinic visit with physical examination will be 6 weeks after chemoradiation, thereafter three monthly during year 1, six monthly during the years 2 and 3 and annually for years 4 and 5
4.4. Late radiotherapy toxicity (greater than 12 months after treatment)

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Uracil and ftorafur (UFT), cetuximab, gemcitabine, capecitabine

Primary outcome(s)
One-year overall survival rate

Key secondary outcome(s))
1. Radiological response evaluation: CT thorax, abdomen and pelvis after neo-adjuvant chemotherapy before randomisation and 6 weeks after completion of chemoradiation. Responses will be assessed in accordance with the Response Evaluation Criteria for Solid Tumours (RECIST).
2. Tumour marker CA19-9: this will be measured at baseline and four weekly during neo-adjuvant chemotherapy, at randomisation and 6 weeks after completion of chemoradiation, and

thereafter at each clinic follow-up appointment.
3. Progression free survival (PFS):
3.1. PFS-registration will be measured from date of registration to date of first appearance of disease progression, relapse, or death from any cause; patients alive without progression or relapse will be censored at date last known to be alive.
3.2. PFS-randomisation will be measured from date of randomisation to date of first appearance of disease progression, relapse, or death from any cause; patients alive without progression or relapse will be censored at date last known to be alive.
4. Overall survival: this will be measured from date of registration to date of death from any cause; surviving patients will be censored at date last known to be alive.
5. Toxicity: this will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 during neo-adjuvant chemotherapy and during chemoradiation. Late radiotherapy toxicity (greater than 12 months after treatment) will be assessed using CTCAE version 3.0.
6. Quality of life: this will be evaluated using the EORTC QLQ C30 (Version 3) and PAN26 module. It will be evaluated at baseline, at 12 weeks (after neo-adjuvant chemotherapy) and at 24 weeks (6 weeks after chemoradiation). It will then be evaluated three monthly during year 1, six monthly during the years 2 and 3 and annually for years 4 and 5.

Completion date
01/03/2014

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Aged greater than or equal to 18 years, either sex
2. Histological or cytological diagnosis of adeno- or undifferentiated non-small cell carcinoma of pancreas
3. Considered to be unresectable based on at least one of the following:
3.1. Extensive peri-pancreatic lymph node involvement
3.2. Encasement or occlusion of the superior mesenteric vein (SMV) or SMV/portal vein confluence
3.3. Direct involvement of superior mesenteric artery (SMA), coeliac axis, inferior vena cava (IVC) or aorta
4. World Health Organization (WHO) performance status 0 - 2
5. No evidence of metastatic disease as determined by computed tomography (CT) scan (chest, abdomen and pelvis) or other investigations
6. Adequate bone marrow function with platelets greater than or equal to 100 x 10^9/l, white blood cells (WBC) greater than or equal to 3 x 10^9/l and neutrophils greater than or equal to 1.5 x 10^9/l
7. Serum bilirubin less than 1.5 x upper limit of institutional normal range (ULN) and transaminases less than or equal to 2.5 x ULN
8. Calculated/measured glomerular filtration rate (GFR) greater than or equal to 50 ml/min (either calculated by Cockcroft and Gault formula or measured as per usual local procedure)
9. No concurrent uncontrolled medical condition
10. No active malignant disease other than non-melanotic skin cancer or carcinoma in situ of the uterine cervix in the last 10 years
11. Life expectancy greater than 3 months

12. Adequate contraceptive precautions if relevant
13. Informed written consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Medical or psychiatric conditions that compromise the patient's ability to give informed consent
2. Presence of metastatic disease
3. Concurrent uncontrolled medical conditions
4. Any previous chemotherapy or radiotherapy, and any investigational treatment for advanced pancreatic cancer
5. Adjuvant chemotherapy with fluoropyrimidine or gemcitabine within 12 months of trial entry
6. Adjuvant radiotherapy with or without chemotherapy for pancreatic cancer
7. Pregnancy or breast feeding
8. Patients with known malabsorption syndromes or a lack of physical integrity of the upper gastrointestinal tract
9. Patients with a known hypersensitivity to 5-FU or with a dihydropyrimidine dehydrogenase (DPD) deficiency
10. Clinically significant (i.e. active) cardiovascular disease. This includes, but is not limited to, the following examples:
10.1. Cerebrovascular accidents (less than or equal to 6 months prior to registration)
10.2. Myocardial infarction (less than or equal to 1 year prior to registration)
10.3. Uncontrolled hypertension (greater than 150/100 mmHg) while receiving chronic medication
10.4. Unstable angina
10.5. New York Heart Association (NYHA) Grade II or greater congestive heart failure
10.6. Serious cardiac arrhythmia requiring medication
10.7. Clinically significant electrocardiogram (ECG) findings (e.g. QTc greater than or equal to 440 msecs [male] 460 msecs [female] or greater than or equal to 2° AV Block, etc.).

Patients who suffer from serious cardiac arrhythmia requiring medication can enter the study only if they are considered to be in a stable condition regarding both the arrhythmia and their medication. Patients with pacemakers are allowed to enter the study only if they are considered as being in a stable condition. In case of doubt, the investigator should obtain a consultation with a local cardiologist.

Date of first enrolment

01/03/2009

Date of final enrolment
30/06/2013

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Royal Marsden NHS Foundation Trust
Sutton
United Kingdom
SM2 5PT

Sponsor information

Organisation
Royal Marsden NHS Foundation Trust (UK)

ROR
https://ror.org/0008wzh48

Funder(s)

Funder type
Industry

Funder Name
Merck Sharp & Dohme Ltd (MSD) (UK)

Funder Name
Royal Marsden NHS Foundation Trust (UK)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	15/03/2016		Yes	No