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The efficacy of epirubicin, cisplatin and capecitabine in carcinomas of unknown primary origin (CUP): prospective validation of diagnosis, classfication and metabolic responses

Submission date 01/02/2011	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 02/02/2011	**Overall study status** Completed	
Last Edited 14/10/2020	**Condition category** Cancer	

Plain English summary of protocol
http://cancerhelp.cancerresearchuk.org/trials/a-trial-of-chemotherapy-cancer-unknown-primary-cup-one

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2008-000657-35

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
MI67

Study information

Scientific Title
A multicentre phase II trial to assess the efficacy of epirubicin, cisplatin and capecitabine in carcinomas of unknown primary origin (CUP): incorporating the prospective validation of molecular classifiers in diagnosis and classification and exploratory metabonomics

Acronym
CUP ONE

Study objectives
Carcinomas of unknown primary origin (CUP) constitute 3 - 10% of all cancer diagnosis, and ranks among the top ten commonest malignancies. The prognosis of these patients is poor, with a median survival of 8 - 12 months from diagnosis. Post-mortem analysis of CUP patients suggest that the commonest primaries found are in the pancreas and lung (accounting for 40%).

There are few clinical treatment studies of CUP, and therefore no consensus on treatment standards. Epirubicin, cisplatin and 5-fluorouracil (ECF) chemotherapy regimen is commonly used in CUP, due to its broad spectrum activity against a variety of known primary cancers, including pancreas, lung and other gastro-intestinal (GI) cancers. Epirubicin, cisplatin and capecitabine (ECX) regimen has recently been confirmed as an equivalent alternative to ECF in gastro-oesphageal cancers. It is superior in terms of tolerability and treatment related complications.

A large variety of cancers have abnormalities, including overexpression, of molecular pathways involved in promoting abnormal cell growth and metastasis, such as the epidermal growth factor receptors (EGFR) and the vascular endothelial growth factor (VEGF). Inhibitors of EGFR activity, for example, have over the last two years shown clinical efficacy and survival benefits in pancreatic, lung, breast and head and neck cancers in particular. These have yet to be systematically investigated in CUP. These signalling pathways may be potentially critical in CUP, as many cases are thought to have a primary originating in the pancreas, lung or GI tract. The EGFR pathway is also dysregulated in studies of CUP tissue.

CUP is a neglected research entity despite its relative frequency. As it presents with metastasis by definition, it is distinguished by its aggressive progression. Further studies are therefore necessary to study the biology of these heterogeneous cancers. This study allows for multiple translational components to be established. Tissues from CUP biopsies will be used to identify molecular characteristics and so the potential sites of the primary cancer, as well as in the analysis of the distinguishing biological nature of these cancers. The laboratory component will incorporate three methods for site of origin classification including two mRNA transcriptional profiling methods, using either microarray (expression profiling discovery microarrays) or real-time polymerase chain reaction (RT-PCR) in addition to one immunohistochemistry based analysis; and metabonomic analysis of blood and urine (exploratory analysis).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Riverside Research Ethics Committee, 08/10/2008, ref: 08/H0706/61

Study design
Multicentre non-randomised non-controlled exploratory phase II trial

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Carcinoma of unknown primary origin (CUP)

Interventions
Treatment will be planned for 8 cycles over 24 weeks with radiological assessments at 12 weeks and 24 weeks or if clinically indicated. Patients progressing or intolerant of trial therapy will discontinue study treatment. Second-line therapy may be offered but is not mandated in this study.

1. Epirubicin: 50 mg/m2 intravenous (IV) bolus once every 3 weeks (maximum 8 cycles)
2. Cisplatin: 60 mg/m2 with hydration (see below) once every 3 weeks (maximum 8 cycles)
3. Capecitabine: 1000 mg/m2 daily in 2 divided doses for 24 weeks

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Epirubicin, cisplatin, capecitabine

Primary outcome measure
1. Translational: To select the molecular classifier with the highest diagnostic accuracy
2. Clinical Trial: To estimate the response rate from the ECX regimen

Outcomes measured retrospectively. There is an efficacy analysis of response when 24 patients are recruited to Clinical Trial (Part 2 of the study).

Secondary outcome measures
Clinical Trial:
1. Progression-free survival
2. Overall survival
3. Quality of life analysis
4. Cost-utility comparison of diagnostic molecular classifiers with average clinical diagnostic work-up
5. Correlation of molecular profiles with patient outcome
6. Identification of potential prognostic metabonomic signatures to efficacy and toxicity profiles

Outcomes measured retrospectively. There is an efficacy analysis of response when 24 patients are recruited to Clinical Trial (Part 2 of the study).

Overall study start date
30/04/2010

Completion date
30/10/2013

Eligibility

Key inclusion criteria
Translational Registration (part 1):
1. Uncertain or unknown primary site of origin of malignancy. This includes patients with a suspected primary site (on history, histology or radiology) but as yet unconfirmed.
2. Histologically confirmed carcinomas (adenocarcinomas, squamous cell carcinoma [SCC] and undifferentiated are all acceptable) from tru-cut biopsy and/or operative procedure
3. Lymphomas, sarcomas, germ-cell tumours are not intended to be either part of this trial, if uncertain or equivocal they can be discussed with the Trial Management Group (TMG)
4. Cytologically confirmed carcinomas, in which a primary cannot be found following appropriate investigations, can only be offered the translational part of the study if either a subsequent tru-cut biopsy, or an operative procedure is to be performed at some stage of the patients investigations or surgical treatment (such as debulking or bypass surgery)
5. Cytologically confirmed carcinomas, in which a primary cannot be found following appropriate investigations, can however still be offered the clinical part of the study
6. Written informed consent is required for both parts separately

Clinical Trial Registration for ECX treatment (part 2):
1. Histologically or cytologically confirmed carcinomas, in which a primary cannot be conclusively identified following appropriate investigations and discussion in the appropriate MDM:
1.1. Lymphomas, sarcomas and germ-cell tumours are not intended to be part of this trial, if uncertain or equivocal they can be discussed with the TMG
1.2. Cytologically confirmed carcinomas, in which a primary cannot be found following appropriate investigations, can be offered both parts of the study only if either a subsequent tru-cut biopsy and/or operative procedure is to be performed at some stage of the patient's investigations or surgical treatment (such as debulking or bypass surgery). Written informed consent is required for both parts separately.
1.3. If only cytological confirmation from a FNA is possible, only the second part of the study can be considered
2. Inoperable metastatic carcinoma with at least unidimensional measurable disease
3. Aged less than 18 years

4. Performance status less than 2
5. Life expectancy greater than 12 weeks
6. Adequate haematological function: absolute neutrophil count less than 2.0 x 10^9/l, white cell count less than 3.0 x 10^9/l, platelets less than 100 x 10^9/l
7. Adequate calculated or measured renal function: serum creatinine less than 120 mg/dl and creatinine clearance greater than 60 ml/min (renal function assessed by either 24 hour creatinine or EDTA clearance, is often more accurate than calculated clearances which can underestimate the true clearance)
8. Adequate hepatic function: bilirubin within 2 x normal range, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 5 times the upper limit of normal
9. Written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Translational = 200 - 400; clinical trial = 57

Total final enrolment
59

Key exclusion criteria
Translational Registration (part 1):
1. Significant intercurrent medical or psychiatric illness which in the opinion of the investigator would compromise the patient's ability to give informed consent
2. Non-carcinoma histology (lymphomas, sarcomas and germ-cell tumours are not intended to be part of this trial; if equivocal discuss with TMG)

Clinical Trial Registration for ECX treatment (part 2):
1. Previous chemotherapy
2. Co-existent second malignancy or history of prior malignancy within 5 years, except for adequately treated basal cell carcinoma and non-invasive carcinoma of the cervix. If history of prior malignancy within 10 years, the previous histology should be compared and available for central review.
3. Pregnant or lactating women. Women of child bearing potential not prepared to use effective contraception.
4. Significant intercurrent medical or psychiatric illness which in the opinion of the investigator would compromise the patient's ability to give informed consent or tolerate the therapy
5. Uncontrolled angina pectoris, heart failure, clinically significant uncontrolled cardiac arrhythmias, or any patient with a clinically significant abnormal electrocardiogram (ECG) or cardiac history having a left ventricular ejection fraction (LVEF) of lower limit of normal range

for institution as determined by multiple gated acquisition (MUGA) scan or echocardiogram
6. The presence of proven cerebral metastases
7. Any chemotherapy, hormonal or immunotherapy or other investigational drug within the preceding 4 weeks (steroids are permissible)
8. Previous radiotherapy is allowed but not to sites of assessable disease. No chemotherapy is to be given until resolution of all acute radiotherapy effects or a minimum of 6 weeks has elapsed since end of radiotherapy. Radiosensitisation with chemotherapy during radiotherapy is not allowed.
9. Hearing difficulties which in the investigators opinion, might significantly worsen with cisplatin therapy

Date of first enrolment
30/04/2010

Date of final enrolment
30/10/2013

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Hammersmith Hospital
London
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W12 0HS

Sponsor information

Organisation
NHS Greater Glasgow and Clyde (UK)

Sponsor details
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Sponsor type
Government

Website
http://www.nhsggc.org.uk

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (CRUK) (UK) - Clinical Trials Advisory and Awards Committee (CTAAC) and Translational Research in Clinical Trials Committee (TRICC) grant awards

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			28/05/2020	No	No
Plain English results			14/10/2020	No	Yes
HRA research summary			28/06/2023	No	No