Capecitabine compared with surveillance in curatively resected biliary tract cancer (BILCAP): a randomised, controlled, phase 3 study

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Abstract

Background: Despite improvements in multidisciplinary management, biliary tract cancer has a poor outcome. Only 20% of cases are suitable for curative surgical resection with a 5-year survival of less than 10% for all patients. No studies have described a benefit for adjuvant therapy. We aimed to determine whether adjuvant capecitabine improved overall survival (OS) compared to observation following surgery for biliary tract cancer.

Methods: A randomised phase III multicentre study recruited across 44 UK centres between 15th March 2006 and 4th December 2014· 753 patients were screened of whom 447 were randomised. Patients were aged 18 years or over with histologically confirmed cholangiocarcinoma or muscle invasive gallbladder cancer who had a macroscopically complete resection performed with curative intent. The ECOG Performance Status had to be < 2 and adequate renal, haematological and liver function was required. Patients were randomised 1:1 to receive capecitabine (1250mg/m2 bid D1-14 every 21 days, for 8 cycles) or observation commencing within 16 weeks of surgery. The primary outcome was overall survival, calculated from the date of randomisation until the date of death or date last known to be alive for surviving patients. Secondary outcomes were recurrence-free survival (RFS), quality of life (QoL) according to QLQ-C30 and QLC-LMC21, toxicity, and health economics. Further planned evaluations were sensitivity and subgroup analyses.

Results: 447 patients with curative resected biliary tract cancer were randomised, 223 to capecitabine and 224 to observation. The data motoring committee advised that final analysis should be performed once 234 events were observed, rather than the 270 originally planned. The median ITT OS was 51·1 months (95%-CI 34·6, 59·1) in the capecitabine group compared with 36·4 (95%-CI 29·7, 44·5) for the observation group (adjusted OS HR 0·80 95%CI 0·63, 1·04; p=0·097). Adjusting for further prognostic factors in a sensitivity analysis the HR was 0·71 (95%CI 0·55-0·92; p=0·010). In the pre-specified per-protocol analysis (capecitabine n=210, observation n=220) the median OS was 53 months (95%CI 40, NR) for capecitabine and 36 months (95%CI 30, 44) for observation (adjusted OS HR 0·75 95%CI 0·58, 0·97; p=0·028). Median RFS (ITT) was 24·4 months (95%-CI 18·6, 35·9) for capecitabine, and 17·5 months (95%-CI 12·0, 23·8) for observation. Of 213 patients that received at least one cycle, 95 (44·6%) had at least one grade 3 or 4 toxicity, of those, the most frequent being hand-foot syndrome in 43 (20·2%), diarrhoea in 16 (7·5%) and fatigue in 16 (7·5%). None of the capecitabine SAEs, and three (10·3%) of those reported in the observation group resulted in death. QoL analysis demonstrated minimal differences between capecitabine and observation arms. The incremental cost per QALY was calculated as £2,725 (US$3,538).

Conclusions: While the trial did not meet its primary endpoint, the sensitivity and secondary analyses strongly support that capecitabine improves overall survival in resected biliary tract cancer when used as adjuvant chemotherapy following surgery and should be considered as standard of care.

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Introduction

Biliary tract cancer (BTC) is an uncommon cancer in developed countries. There are approximately 1200 and 9000 new cases per year in the United Kingdom and United States. (1, 2) The incidence is increasing, perhaps associated with increasing gallstone disease. Curative resection is feasible in 20% of presenting patients (3) and increasing centralisation of often complex surgery in specialist hepatopancreatobiliary (HPB) centres aims to improve outcome. (4) (5) The post-operative median survival is reported at 18-30 months, with node-positive and margin-positive patients faring less well. (6)

The standard of care for patients with un-resectable BTC has been established suggesting that BTC are chemo-responsive malignancies. (7) (8) However the value of adjuvant chemotherapy has not been effectively investigated. A subgroup of the ESPAC-3 trial comprising 96 patients with biliary tract cancer (9) and the study by Takada (133 patients including non-curative BTC resections) (10) were not sufficiently statistically powered to define a standard of care. More recently, a randomised study of gemcitabine compared to surveillance in 225 patients with curatively resected extrahepatic peri-hilar cholangiocarcinoma was negative for overall survival (HR 1·01, 95% CI 0·70-1·44, p=0·97). (11) In addition a phase 3 trial testing adjuvant oxaliplatin and gemcitabine compared to surveillance has recently been reported. The outcome was not significant for overall survival (HR 1·08 95%C: 0·70 1·66 (p = 0·74)) however a large effect size was seen (50·8m vs 75·8m) for chemotherapy. (12) A meta-analysis of mostly non-randomised series has suggested potential benefit for chemotherapy as adjuvant therapy in node-positive disease and radiation-based adjuvant therapy in resection margin-involved (R1) subgroups but these are unproven hypotheses. (13)

Capecitabine is an oral fluoropyrimidine pro-drug effective as adjuvant chemotherapy treatment, either alone or in combination, in colorectal, (14) oesophagogastric (15) and pancreatic (9) malignancies. Fluoropyrimidines have evidence of activity in BTC, (10) are well tolerated and used in everyday oncological practice. Although supportive clinical data are limited, feasibility and compliance with treatment were critical in this study and capecitabine was selected. A trial of capecitabine compared to observation following resection of biliary tract cancer (BILCAP) was undertaken in specialist HPB centres in the UK.

Methods

Randomisation and Masking

Masking was not performed and allocation concealment was achieved using a computerised minimisation algorithm that stratified on surgical centre, site of disease, resection status and performance status. Concealment remained until the interventions were assigned by a central telephone based randomisation service hosted by Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham.

Study Interventions

Patients were randomised 1:1 to receive oral capecitabine 1250mg/m^2 bid post-operatively twice a day on day 1 to 14 of a 3-weekly cycle for 24 weeks or observation. Following randomisation chemotherapy was started soon as possible after surgery and up to 12 weeks from surgery, with a maximum of extending to 16 weeks from surgery.

Follow Up

The follow up comprised computerised tomography (CT) every 6 months for the first 24 months, further CT at annual intervals with clinical review up to 5 years, conducted 3 monthly in year 1, 6 monthly in year 2 and annually thereafter.

Inclusion/ Exclusion Criteria

Patients were aged 18 years or over with histologically confirmed cholangiocarcinoma (CC) or muscle invasive gallbladder cancer (GBC) who had a macroscopically complete resection with curative intent were eligible. All patients should have had radical surgical treatment which includes liver resection, pancreatic resection or, less commonly, both. The ECOG Performance Status had to be < 2 and adequate renal, haematological and liver function was required. Patients with pancreatic or ampullary cancer, mucosal GBC, or who had not completely recovered from previous surgery, or had unresolved biliary tree obstruction or those who had previous chemotherapy or radiotherapy for biliary tract cancer were ineligible. Criteria are described in full in the study protocol (ISRCTN: 72785446) (http://www.birmingham.ac.uk/research/activity/mds/trials/crctu/trials/bilcap/index.aspx and appendix).

All surgery was undertaken in specialist HPB centres, mandated in the UK. The surgical strategy was to achieve complete microscopic clearance of the disease including liver or pancreatic resection. Patients with less than 1mm clearance were classified as R1 patients. Those with intra-hepatic CC underwent hepatectomy and lymphadenectomy was not mandated. In the case of hilar CC, hepatectomy including segment 1 was performed along with radical excision of the extrahepatic biliary tree. Lymphadenectomy was performed in accordance with local practice. Patients with muscle-invasive GBC were treated by

cholecystectomy (when the gallbladder was in situ) and hepatectomy including the gallbladder bed. Excision of the extrahepatic biliary tree and the extent of lymphadenectomy was dependent on local practise. Biliary tract excision was commonly performed where the cystic duct had been involved by tumour. For tumours in the lower common bile duct, pancreaticoduodenectomy (Whipple's procedure) with excision of the extrahepatic biliary tree and a standard lymphadenectomy was performed.

Outcome measures

The primary outcome measure, overall survival (OS), was calculated from the date of randomisation until the date of death or date last known to be alive for surviving patients. Pre-specified secondary outcome measures included a per-protocol analysis, relapse-free survival (RFS), toxicity, health economics (HE), and quality of life (QoL). RFS was measured from randomisation until the date of disease recurrence, death from disease or date of last trial follow-up. Toxicity was categorized according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events version 3·0, QoL, recorded over 24 months, was measured using the European Organisation for the Research and Treatment of Cancer (EORTC) quality of life questionnaires QLQ-C30 and QLC-LMC21, designed for all cancer patients and patients with colorectal liver metastases respectively. Long term outcome measures will be reported elsewhere once all surviving patients have minimum follow-up of 60 months.

Sample size

The initial sample size calculation was based on the assumption that the 24-month survival would be 20% in the observation arm, 5 and that treatment with capecitabine would

improve this rate by 12% to 32%. As such 360 patients and 270 events were needed to detect a HR of 0·71 with 2-sided significance level of 5% and 80% power. The independent data monitoring committee (IDMC) met annually to review safety data and trial progress; no formal interim analyses were performed. It became clear during the IDMC meeting of July 2013 (at which point 364 patients had been recruited) that the observed event rate was less than originally estimated. Based on this the IDMC recommended that the final analyses be performed to once 234 events had accrued. This permitted detection of an increase in OS 60% to 71% (HR 0·69); a marginally larger effect than originally planned. The IDMC instructed that screening ceased in September 2014, and recruitment in December 2014· Analyses were performed once the protocol-specified minimum follow-up period was complete.

Analyses

Analyses were performed according to the statistical analysis plan (SAP, see web appendix). Primary analyses were performed on an intention-to-treat (ITT) basis, including all randomised patients. Analyses were also performed on a per-protocol (PP) population which excluded ineligible patients and those failing to complete at least one cycle of capecitabine (PP analyses were pre-specified in the SAP and not the protocol). The safety population comprised any patient receiving at least one dose of capecitabine. Both arms were monitored for safety and Serious Adverse Event (SAE) reporting was captured up to a maximum of nine months from randomisation. With no specific intervention delivered, adverse events (AEs) for toxicity were not monitored in the observation arm.

Survival differences were quantified as hazard ratios (HRs) with 95%-confidence intervals (CIs) estimated using Cox proportional-hazards model with adjustment for minimisation factors. Analyses were not adjusted for surgical centre due to the large number participating centres (n=36) leading to flat statistical modelling regions. Additionally sensitivity analyses of OS and RFS were performed on the ITT population adjusting the treatment effect on OS and RFS for identified prognostic factors (see web appendix page 2). Analyses of Schoenfeld residuals assessed the proportional hazards assumption for OS and RFS, and time varying effects (TVE) were modelled when the assumption did not hold, with specification of TVEs guided by visual inspection of -log(-log(S(t))) plots, where S(t) is the survival probability at time *t*. Pre-planned subgroup analyses were performed using adjusted Cox models with heterogeneity tested via interaction terms. Subgroups were: age (60 years); sex; tumour size (50mm); nodal status; tumour stage; disease grade; ECOG; resection status; site of disease. Each QOL domain was assessed through comparison of standardised area under curve (SAUC) via a Mann-Whitney test. Economic analysis estimated incremental cost per Quality Adjusted Life-Year (QALY), based OS and quality of life (EQ5D). Costs included intervention plus NHS service use. Economic analyses were adjusted for baseline values, and uncertainty assessed through cost-effectiveness acceptability curves.

All analyses were performed in Stata version 14. No adjustment for multiplicity was made.

Sponsor

This randomised phase 3 study was run by the Cancer Research UK Clinical Trials Unit, University of Birmingham under the auspices of the National Cancer Research Institute Upper Gastrointestinal Cancer Studies Group of the UK and sponsored by the University of

Southampton. This trial was approved by the West Midlands Multi-Centre Research Ethics Committee (05/MRE07/62) and all necessary regulatory approvals were obtained. All patients were required to give written informed consent and the trial was conducted in accordance with the Declaration of Helsinki and the CONSORT (http://www.consort-statement.org/) and CHEERS(16) guidelines. An independent data monitoring committee reviewed the data. No formal interim analyses were planned or performed.

Major protocol amendments included extending the start date of chemotherapy from 8 to 12 weeks from the date of definitive surgery in October 2007, a further extension to 16 weeks post-op and the inclusion of extra-hepatic CC following the completion of the ESPAC-3 study in August 2008· These recommendations were based on monitoring of the accumulating events rather than repeated interim analyses. The study was funded by Cancer Research UK. An unrestricted educational grant was given by Roche, supporting recruitment and collection of translational material, who had no part in the running or analysis of the study.

Results

Seven hundred and fifty-three patients were screened of whom four hundred and forty-seven patients (ITT population) were randomised to capecitabine (n=223) or observation (n=224) from 44 UK centres between 15th March 2006 and 4th December 2014 (Figure 1). The PP population comprised 430 patients (210 capecitabine and 220 observation) following the exclusion of 17 patients comprising 8 (1·8%) patients (four in each arm) who were found to be ineligible after randomisation and 10 (2·2%) who did not receive capecitabine (web

appendix page 1). One patient was ineligible and also received no drug. The required minimum follow-up of 24 months was reached in January 2017 when the median (IQR) follow up in surviving patients was 53·8 months (35·7, 82·1).

Baseline characteristics were well balanced between the two groups (Table 1). Of the 447 patients, most common were 156 (34·9%) lower common bile duct CC, followed by hilar 128 (28·6%), 84 (18·8%) intrahepatic CC and 79 (17·7%) GBC respectively. The resection margin was positive (R1) in 168 (37·6%) of patients and 437 (97.8%) of patients were performance status 0 or 1. Lymph node status was negative (N0) in 236 (52.7%). The median (IQR) weeks from surgery to randomisation was 10·3 (8·4, 12·1) and 10·4 (9·0, 12·1) in the capecitabine and observation arms respectively.

At the time of the final analysis, death had been observed in 114 (51·1%) of 223 capecitabine and 131 (58·5%) of 224 observation patients, totalling 245· Of these, 241 (98·4%) were BTC related with reasons unknown in 2 and 'other' in 2 further patients (web appendix page 1). The median ITT OS for capecitabine was 51·1 months (95%-CI 34·6, 59·1), and 36·4 (95%-CI 29·7, 44·5) for observation OS HR 0·81 (95%CI 0·63, 1·04; p=0·097) (Figure 2A) for those treated with capecitabine when adjusted for minimisation factors other than surgical centre. The 24-month ITT OS was 71·9% (95%-CI 56·0, 68·8) and 62·8% (95%-CI 65·4, 77·4) for capecitabine and observation respectively. Planned sensitivity analyses in the ITT population explored the impact of identified prognostic factors (nodal status, grade of disease and gender). Adjusting for these and minimisation factors resulted in an OS HR of 0·71 (95%-CI 0·55, 0·92; p=0·0095). In the per-protocol analysis (Figure 2B), the median OS

was 52·7 months (95%-CI 4ĈI0·3, NR) for capecitabine and 36 months (95%CI 30, 44) for observation (adjusted OS HR 0·75 95%CI 0·58, 0·97; p=0·028).

In total 280 (62·6%) patients experienced disease recurrence, with 114 (51·1%) of 223 capecitabine and 131 (58·5%) of 224 observation patients. Median ITT RFS was 24·4 months (95%-CI 18·6, 35·9) for capecitabine, and 17·5 months (95%-CI 12·0, 23·8) for observation (Figure 3A). The relative difference in risk between treatment groups differed over time and as such Cox models with time varying effects were fitted. The adjusted RFS HR was 0·75 (95%-CI 0·58, 0·98; p=0·033) in the first 24 months from randomisation, with no evidence of a difference in the period from 24 to 60 months (RFS HR 1·48 (95%-CI 0·80, 2·77); p=0·21). In the per-protocol analyses the median RFS was 25·9 months (95%-CI 19·8, 46·3) for capecitabine and 17·4 months (95%-CI 12·0, 23·7) for observation (Figure 3B). The adjusted RFS HR from 0 to 24 months was 0·70 (95%-CI 0·54, 0·92; p=0·0093) and there was no evidence of a difference beyond 24 months (RFS HR 1·55 (95%-CI 0·82, 2·93); p=0·18, see web appendix pages 1 to 3 for final OS and RFS models).

The median (IQR) capecitabine dose was 1250·0 mg/m^2 bid (1060·9, 1250·0). All but 10 (4·5%) patients who started capecitabine received at least one cycle of capecitabine and 122 (54·7%) completed eight cycles of capecitabine; of the 213 patients who started treatment, 99 (46·5%) experienced at least one dose reduction. Of the 69 (32·4%) who discontinued due to toxicity, the most common complaints were hand and foot syndrome in 10 (14·0%) patients, gastrointestinal in 9 (12·9%) and other in 21 (31·1%, patients could cite more than one toxicity type).

Adverse events (AEs) were only recorded in the capecitabine group, and serious AEs (SAEs) were recorded in both groups. Treatment toxicity was assessed in the safety population (213 patients), and 212 patients (99·5%) reported 4694 toxicities in total. Grade was unknown in 21 (<1%) events. Of the 213 patients, 95 (44·6%) had at least one grade 3 or 4 toxicity (Table 2). The most frequent grade 3 and 4 events were hand-foot syndrome in 43 patients (20·2%), diarrhoea in 16 (7·5%) or fatigue in 16 (7·5%) of 213 patients. SAEs were observed in 47 (21·1%) of 223 capecitabine patients (64 events) and 22 (9·8%) of 224 observation patients (29 events). Of the 64 capecitabine SAEs, 33 (51·6%) were related to treatment, and of those, five (7·8%) were cardiac events related to capecitabine (Table 3). None of the capecitabine SAEs, and three (10·3%) of those reported in the observation group resulted in death due to BTC (web appendix page 4).

Subgroup analyses of clinical factors are presented in the forest plot (Figure 4). In the ITT population, benefit was indicated in men (HR 0·70 (95%-CI 0·50, 0·99)) and those with poorly differentiated disease (HR 0·60 (95%-CI 0·39, 0·93)). There was a trend towards greater benefit of treatment in younger patients, stage 2 and performance status 0 patients, tumours with negative margins, and lower common bile duct CC. There was no statistical evidence of heterogeneity.

In total 1915 QoL questionnaires were returned by 433 (96·9%) of 447 patients. Area under curve was standardised by time and hence SAUC is interpreted as the average monthly QoL. The full set of results is provided in Table 3· Statistically significant differences were observed for QLQ-C30 which demonstrated a reduction in social functioning (p=0·01) with median (IQR) 76·2 (56·9, 91·7) and 83·3 (64·6, 95·8) respectively for capecitabine and

observation. And for LMC-21 which identified increased taste symptoms (p=0·04) with SAUC 0·0 (0·0, 11·1) and 0·0 (0·0, 6·3), and peripheral neuropathy (p=0·01) in the capecitabine group with SAUC 0·0 (0·0, 13·5) and 0·0 (0·0, 4·2), although the latter should be interpreted as hand-foot syndrome. These differences in QoL have no clinical significance. No other statistically significant differences were observed (Table 4).

The mean QALY gain at two years was 0·04 leading to an incremental cost per QALY of just under £13,300 (US $17,200). Linear extrapolation to 5 years reduced the incremental cost per QALY to £2,725 (US$3,538). The cost effectiveness acceptability curve indicated a probability of over 90% of capecitabine being cost effective at willingness to pay above £18,000 (US$23,377, see cost-effectiveness acceptability curve; web appendix page 4).

Discussion

The BILCAP study, which compared capecitabine to observation as adjuvant in curatively resected biliary tract cancer provides evidence that capecitabine can improve overall survival. Although the ITT OS primary endpoint did not reach statistical significance, the sensitivity analyses of the ITT population, the PP OS analysis and the RFS were positive and the OS effect size of 14·7 months is clinically meaningful. The ITT (statistically negative) and PP (statistically positive) populations differed by 17 patients who were either found to be ineligible or were randomised to but did not receive capecitabine. Of those that did not receive capecitabine, the most common reason cited was the patient no longer wished to participate in the trial (web appendix page 1).

The ITT and PP analyses revealed no evidence of a difference in RFS in the period between 24 and 60 months, suggesting deferred recurrence rather than cure. This will be explored in the long-term survival measures to be reported once 5 years of follow-up has been met.

The limitations of this study include the long recruitment period of 10 years during which time approaches to clinical trial process have become more defined. An unintended consequence is that the protocol, acceptable when written in 2005, can be criticised. Additionally, the heterogeneity of biliary tract cancers, both surgically and more recently, biologically, makes an overall interpretation more complex. Additionally surgical centre was not included in the modelling analyses adjusted for minimisation factors.

Adverse events were modest and the incidence of some potentially-serious toxicities such as fluoropyrimidine related cardiac vasospasm were significantly less than seen in similar studies, perhaps because any serious cardiac co-morbidity had been unmasked in preparation for and during HPB surgery. Although some significant changes in QoL were observed, the differences were modest and support a tolerable and deliverable regimen which is cost effective. Compliance to capecitabine in BILCAP was lower than for colorectal cancer (14) but equivalent to that for patients having had HPB surgery. (9) Further analysis of dose intensity to determine any impact on outcome will be reported elsewhere.

We have reported median survivals of over 50 months following curative surgery for BTC, an improvement upon historical controls likely to be a reflection of improved surgical selection and management as well as the fitness required for clinical study. Centralisation in the care of complex medicine has resulted in improved outcomes, (5) specifically for cancer surgery and has been the principle behind the establishment of specialist HPB centres in the UK.

This improvement became apparent during recruitment and required a protocol amendment changing the observed 2-year survival on the observation arm from 20% to 60%. Additionally, during the recruitment period, the standard of care in advanced disease was established and this may have impacted on the unanticipated improved survival. (7, 8)

Biliary tract cancer is an uncommon cancer and as witnessed by the study duration and required adaptations to BILCAP as well as the experience of other investigators, adjuvant studies are challenging. Although BILCAP was not a statistically positive study by the primary ITT analysis, the position of equipoise amongst oncologists may be sufficiently impacted by the weight of the overall positive body of BILCAP data as to render a future study with an observation arm unfeasible. We note the control arm in the current European adjuvant study has been changed to capecitabine from observation perhaps for this reason. (17) We believe the body of BILCAP data as a whole is sufficient to propose a benefit for adjuvant capecitabine as a standard of care in the adjuvant management of curatively resected biliary tract cancer.

BTC is emerging as a biologically heterogeneous group of cancers (18) which perhaps explains the failure of targeted therapies in unselected patient populations to demonstrate benefit in advanced disease (19) (20) (21) although there is promise in selected populations. (22) (23) The translational research outcomes for BILCAP are therefore critical to the future testing of more effective therapies.

In summary, while the BILCAP study did not meet its primary endpoint, the sensitivity and secondary analyses strongly support that capecitabine improves overall survival in resected

biliary tract cancer when used as adjuvant chemotherapy following surgery and should be considered as standard of care.

Role of funding source

The Cancer Research UK (CRUK) Clinical Trials Unit, University of Birmingham was responsible for study conduct in collaboration with the University of Southampton (sponsor). Upon completion of patient follow-up, JP, RF, CS and JB had full access to all of the data and the corresponding authors had final responsibility to submit for publication. The study was funded by CRUK who otherwise had no role in conducting the study. Roche provided an educational grant to support translational research but otherwise had no role in the running of the study.

Author contributions: JP and JB were responsible for the literature search, study design, data collection, data analysis, data interpretation and writing. RF performed all statistical analyses. RF, DS, CS, JG, DC and JWV were responsible for the study design, data collection, data interpretation and writing. DP, HM, RajP, DM, AA, PC, SF, MF-J, HW, PR, LW, JW, JN, RaajP, YTM, BD and TI were responsible for the data collection, data interpretation and writing. JR and SZ were responsible for the data interpretation and writing. A list of all contributing investigators in provided in web appendix pages 4 and 5·

Conflict of interests: AA, JP, PC, BD, SF, MF-J, RF, JG, HM, DM, JN, DP, RajP, RaajP, JR, DS, CS, LW, HW and SZ have no conflict of interests. JB has received honoraria, speakers' fees and travel support from Roche, Amgen, Merck Serono, Servier, Celgene and MSD. DC has

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Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others by signed data access agreement.

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