Long term outcomes and exploratory analyses of the randomised phase 3 BILCAP study

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Running title: Long term outcomes of the BILCAP phase 3 study

The initial analysis of these data have been published. [1]

Abstract

Purpose

The BILCAP study described a modest benefit for capecitabine as adjuvant therapy for curatively resected biliary tract cancer and capecitabine has become the standard of care. We present the long-term data and novel exploratory subgroup analyses.

Methods

This randomised, controlled, multicentre, phase 3 study recruited patients 18 years or older with histologically confirmed cholangiocarcinoma or muscle-invasive gallbladder cancer following resection with curative intent, and an Eastern Cooperative Oncology Group performance status of less than 2. Patients were randomly assigned 1:1 to receive oral capecitabine (1250 mg/m² twice daily on days 1–14 of a 21-day cycle, for eight cycles) or observation. The primary outcome was overall survival (OS). This study is registered with EudraCT 2005-003318-13.

Results

Between March 15, 2006, and Dec 4, 2014, 447 patients were enrolled; 223 patients with biliary tract cancer resected with curative intent were randomly assigned to the capecitabine group and 224 to the observation group. At the data cut-off of 21 January 2021 the median follow-up

for all patients was 106 months (95% CI 98, 108). In the intention-to-treat analysis, median OS was 49.6 months (95% CI 35.1, 59.1) in the capecitabine group compared with 36 ·1 months (95% CI 29.7, 44.2) in the observation group (adjusted hazard ratio [HR] 0 ·84, 95% CI 0.67, 1.06). In a protocol-specified sensitivity analysis, adjusting for minimisation factors, nodal status, grade, and gender, the OS HR was 0 ·74 (95% CI 0.59, 0.94). We further describe the prognostic impact of R status, grade, nodal status and sex.

Conclusion

This long-term analysis supports the previous analysis, suggesting that capecitabine can improve OS in patients with resected biliary tract cancer when used as adjuvant chemotherapy following surgery and should be considered as standard of care.

Introduction

Biliary tract cancer (BTC) includes intrahepatic cholangiocarcinoma (iCCA), peri-hilar cholangiocarcinoma (pCCA) , gallbladder cancer and distal or lower common bile duct cholangiocarcinoma (dCCA) as described in the ICD11/ICD-O-3 (https://www.who.int/standards/classifications/classification-of-diseases; http://www.iacr.com.fr/). pCCA and dCCA are often also referred to as extrahepatic cholangiocarcinomas. pCCA are associated with liver flukes and iCCA to causes of hepatic insult similar to those for hepatocellar carcinoma but for most, the aetiology is uncertain.[3] The incidence of iCCA is increasing across the western world [2] ; however BTC remain uncommon cancers, often presenting late with a poor outcome. [3] For those 20% of patients presenting with operable disease, the 5 year survival is 25% and those with advanced disease less than 5%.[3]

The BILCAP study was a randomised phase 3 study of oral capecitabine chemotherapy compared to observation alone following curative-resection of BTC and established capecitabine as the adjuvant standard of care in the context of other negative studies. [1 4 5] Although negative for the primary endpoint, the previously presented data were accepted as sufficient to support a recommendation as standard of care by the oncological community in the context of the positive per-protocol analysis, the positive relapse free survival data and the supportive sensitivity analyses. We present the pre-specified long-term (five-year) survival outcomes for the BILCAP study as well as describing novel exploratory analyses.

Methods

These have been previously described [1] but in brief, BILCAP was a randomised, controlled, multicentre, phase 3 study run across 44 centres in the UK. Patients aged18 years or older with histologically-confirmed cholangiocarcinoma or muscle-invasive gallbladder cancer who had a macroscopically complete resection with curative intent were eligible. All patients underwent radical surgical treatment, which included liver resection, pancreatic resection, or, less commonly, both. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) had to be less than 2, and adequate renal, haematological, and liver function was required. Patients with pancreatic or ampullary cancer, mucosal gallbladder cancer, or unresolved biliary tree obstruction were ineligible. Patients who had not completely recovered from previous surgery or who had previous chemotherapy or radiotherapy for BTC were also excluded. Criteria are described in full in the study protocol (appendix 1). The anatomical subgroups have been re-designated according to ICD10 as intrahepatic CC (iCCA), peri-hilar cholangiocarcinoma (pCCA), muscle invasive gall bladder carcinoma (GBC) and lower common bile duct or distal cholangiocarcinoma (dCCA, https://www.who.int/standards/classifications/classification-of-diseases).

Major protocol amendments included extending the start date of chemotherapy from 8 to 12 weeks from the date of definitive surgery on Oct 16, 2007, a further extension of study eligibility to 16 weeks after surgery on Sept 2, 2008, and the inclusion of extrahepatic cholangiocarcinoma following the completion of the ESPAC-3 study[6]on Aug 26, 2008. These recommendations were made by the independent data monitoring committee on the basis of

the accumulating events during blinded patient monitoring rather than due to repeated interim analyses.

Randomisation and masking

Patients were randomly assigned 1:1 to the capecitabine group or the observation group. Treatment was not masked, and allocation concealment was achieved using a computerised minimisation algorithm that stratified patients by 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 the Cancer Research UK Clinical Trials Unit (Birmingham).

Procedures

Oral capecitabine (1250 mg/m^2) was given postoperatively twice a day on days 1 to 14 of a 3-weekly cycle for 24 weeks (eight cycles), and observation commenced within 16 weeks of surgery. Following randomisation, chemotherapy was started as soon as possible but with a maximum of 16 weeks from surgery. The protocol permitted dose modifications and cycle interruptions. In cases in which the capecitabine dose was reduced, it was not subsequently increased for any reason. In the case of dose interruptions due to toxicity for longer than 2 weeks, the patient was considered to be off treatment. There were no criteria for removal of patients from the study. Patients had the option to withdraw from trial treatment or follow-up at any stage. The criteria for early treatment discontinuation included safety concerns, patient

deterioration, and administration of any other cancer treatment during the study treatment period.

All surgery was undertaken in specialist hepatopancreatobiliary (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 1 mm clearance were classified as surgical margin-positive (R1) patients. Patients with intrahepatic cholangiocarcinoma underwent hepatectomy, and lymphadenectomy was not mandated for these patients, consistent with surgical practice at the time. In the case of hilar cholangiocarcinoma, patients underwent hepatectomy, including segment 1, along with radical excision of the extrahepatic biliary tree and standard lymphadenectomy. Patients with muscle-invasive gallbladder cancer 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 practice. Biliary tract excision was commonly performed in patients in whom the tumour involved the cystic duct. For tumours in the lower common bile duct, patients underwent pancreaticoduodenectomy (Whipple's procedure) with excision of the extrahepatic biliary tree and a standard lymphadenectomy.

Computerised tomography (CT) scans were done every 3 months in year 1, every 6 months in year 2, and annually thereafter up to 5 years. Full blood count, biochemistry, and liver function tests were done at baseline, at the beginning of each treatment cycle for the capecitabine group, and every 3 months in year 1 and every 6 months in year 2 for all patients. Follow-up treatment for patients who had disease recurrence was not recorded. Toxicity, quality of life and cost

economic evaluation have been previously described. [1] This trial was run by the Cancer Research UK Clinical Trials Unit, University of Birmingham (UK), under the auspices of the UK National Cancer Research Institute (NCRI) Upper Gastrointestinal Cancer Studies Group and sponsored by the University of Southampton (UK). 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 reported according to CONSORT guidelines.

Outcomes

The primary outcome was overall survival, defined as the time from randomisation until the date of death or last date of follow-up for surviving patients. Pre-specified secondary outcomes included a per-protocol analysis of outcomes, recurrence-free survival, toxicity*, health economics*, and quality of life* (*not described here). Recurrence-free survival was defined as the time from randomisation until the date of disease recurrence, death from disease, or date of last follow-up.

Statistical analysis

Details of the statistical analysis were reported previously and the final analysis, as specified in the Statistical Analysis Plan (SAP). Long term follow-up results reported here replicate the analyses used in the initial report. Primary analyses prespecified by protocol were by intention

to treat, including all randomised patients. Analyses were also done by per protocol, excluding ineligible patients and those failing to complete at least one cycle of capecitabine, as specified in the SAP. We quantified overall and recurrence-free survival differences as HRs with 95% CIs estimated using Cox proportional-hazards models with adjustment for minimisation factors. As in the previously reported analysis, we did not adjust by surgical centre because of the number of participating centres (n=44) leading to flat statistical modelling regions.

We also update the pre-specified sensitivity analyses of overall survival in the intention-to-treat population, adjusting for the same prognostic factors as in the previous analysis. Subgroup analysis used Cox models including the minimisation factors primary tumour site, Resection status and ECOG performance status, with heterogeneity tested via interaction terms.

Reporting of the local and distant recurrence rates was descriptive with no hypothesis testing undertaken. Where appropriate (specifically plots with only two arms) we have followed the Kaplan-Meier plot guidelines previously outlined. [7] Analysis was conducted using Stata® 17 software. Full final analysis results were reported previously, as specified in the Statistical Analysis Plan (SAP), and these long-term follow-up results replicate the analyses used in the previously reported results.

Role of the funding source

The funder of the study had an advisory role in study design but no role in the running of the study, data collection, data analysis, data interpretation, or writing of the report. Upon

completion of patient follow-up, JNP, PF and JB had full access to all the data and the corresponding authors had final responsibility for the decision to submit for publication. An educational grant was awarded for translational study purposes by F. Hoffmann-La Roche AG who had no input into the study conduct.

Results

Between March 15, 2006, and Dec 4, 2014, 447 patients (intention-to-treat population) were enrolled and randomly assigned to the capecitabine group (n=223) or the observation group (n=224; supp figure 1). The per-protocol population comprised 430 patients (210 in the capecitabine group and 220 in the observation group) following the exclusion of 17 patients, comprising seven (2%) patients (three in the capecitabine group and four in the observation group) who were found to be ineligible after randomisation, nine (2%) patients who did not receive capecitabine, and one (<1%) patient was ineligible and also received no drug. Baseline characteristics were well balanced between the two groups (table 1).

At the time of this long-term follow-up analysis (21 January 2021), the median follow-up was 106 (95% CI: 98, 108) months. 145 (65%) patients had died in the capecitabine group and 159 (71%) patients had dies in the observation group. Of these deaths, 272 (89%) were related to biliary tract cancer (129 in the capecitabine group and 143 in the observation group), 12 (4%) were from other causes (6 in each group) and 20 (7%) were due to unknown reasons or were missing (10 in each group).

In the intention-to-treat analysis, median overall survival was 49.6 (35.1, 59.1) months for capecitabine and 36.1 (29.7, 44.2) months in the observation group (figure 1a). The hazard ratio (HR) for death of capecitabine versus control was 0.84 (0.67, 1.06,), adjusted for the stratification factors resection status, performance status and site of disease. In the per-protocol analysis (figure 1b), median overall survival was 52.3 (36.5, 63.3) months for capecitabine and 36.1 (29.6, 42.5) months for observation, with an HR of 0.79 (0.63, 1.00), adjusted for the minimisation factors as for the intention-to-treat analysis.

In the intention-to-treat analysis, median recurrence-free survival (RFS) was 24.3 (18.6, 34.6) months for capecitabine and 17.4 (11.8, 23.0) months for surveillance (figure 1c), with a hazard ratio of 0.81 (0.65, 1.01), adjusted for resection status, performance status and site of disease. In the per-protocol analysis, median recurrence-free survival was 25.3 (18.9, 36.7) months for capecitabine and 16.8 (11.8, 20.7) months for (figure 1d), with a hazard ratio of 0.77 (0.61, 0.97), adjusted for resection status, performance status and site of disease. As previously reported, the relative difference in risk between treatment groups differed over time and hence again Cox models with time-varying effects were fitted. The adjusted recurrence-free survival HR was 0.74 (0,57, 0.96) in the first 24 months from randomisation, with insufficient evidence of a difference from 24 months onwards: HR 1.47 (0.86, 2.52). In the per-protocol analysis, the adjusted recurrence-free survival HR in the first 24 months was 0.69 (0.53, 0.90), and again there was insufficient evidence of a difference after 24 months: HR 1.57 (0.90, 2.74).

The 5-year recurrence-free-survival proportion for the intention-to-treat population was 34% (28, 40) for capecitabine and 31% (25, 37) for observation. 306 (68%) of 447 patients had disease recurrence (or death from disease), of whom 147 (66%) were in the capecitabine group and 159 (71%) in the observation group. Of these 306 patients, ten first experienced recurrence (or death from disease) over five years from randomisation. The highest risk of recurrence appears to be at 24 months for both capecitabine and surveillance groups (supp fig 3).

Planned sensitivity analyses in the intention-to-treat population explored the effect of identified prognostic factors (nodal status, grade of disease, and sex, in addition to the minimisation variables site of disease, Resection status and ECOG performance status). Adjusting for these prognostic factors resulted in an overall survival HR for capecitabine of 0.74 (0.59, 0.94) (table 2, figure 2). We observed a significantly poorer survival in the R1 population compared to R0: HR 1.60 (1.25, 2.04), positive node status compared to negative: HR 2.22 (1.74, 2.85), poorly differentiated tumours compared to well differentiated: HR 1.90 91.30, 2.78), and better survival in females compared to males: HR 0.78 (0.61, 0.99). There was no evidence that either site of disease (figure 3), or ECOG performance status, were associated with differential survival (table 2). Recurrence-free survival by disease site is also reported using Kaplan-Meier plots in supplementary figure 2.

Subgroup analysis checked for evidence of a differential treatment effect in some groups, and were reported extensively previously. Visually it appears that poorly differentiated tumours

and male sex are associated with a greater benefit of treatment (figure 2b, 2d respectively), however testing this by modelling interactions indicated no statistical evidence of heterogeneity.

The presence or absence of local and distant recurrence by treatment and resection status was explored and the descriptive results reported in table 3. In the observation arm R1 resections are more likely to have a local recurrence alone (24/84, 29%) compared to R0 resections (27/140, 19%, table 3). Capecitabine did not appear to have any impact on the local recurrence rate for either R0 (26/139 (19%)) or R1 (25/84 (30%)) resections.

Discussion

These long-term data confirm the benefit for capecitabine as adjuvant therapy following surgical resection of biliary tract cancer, which is now recommended by ASCO guidelines. [7] The results support the view that the benefit, although clinically meaningful, is modest and patients and investigators are encouraged to participate in adjuvant studies aimed at improving outcomes further (e.g. the international ACTICCA-01 study (NCT02170090) [8]) which compares capecitabine with the ABC-02 regimen of cisplatin and gemcitabine). [9] The results of the ASCOT study in which patients are randomised to receive S-1 compared to surveillance are also anticipated. [10] These studies will increase the knowledge base of the use of adjuvant fluorpyrimidine in BTC as well as providing valuable material for translational analyses.

BILCAP is the largest prospective randomised dataset in this setting and the control arm offers insights into the natural history of BTC following resection. These data suggest that local recurrence remains a significant issue for up to 50% of all patients following resection, whether the resection is classed as R1 or not, although local recurrence occurs more frequently in patients in R1. The frequency of local recurrence suggests the need to develop novel therapeutic strategies, accepting that more extensive surgery is seldom possible even in the context of expert centres. Neoadjuvant approaches or local therapies such as stereotactic radiotherapy warrant investigation. R1 itself is demonstrated to be a negative prognostic factor as are lymph node involvement, poor differentiation of tumours and male sex. We did not observe any meaningful difference in treatment benefit in subgroups, including nodal status, resection status, or primary disease site. There was some indication that poorly differentiated tumours and male sex were associated with higher treatment benefit, but the evidence was weak and formal statistical testing did not lead to any definitive results. However, as the study was not powered to detect effects in subgroups, more research is recommended. We conclude that capecitabine remains effective and beneficial in this population regardless of subgroup classification.

These data suggest that capecitabine appears to have little impact on local recurrence or local and distant recurrence for both R1 resections and R0 resections. The main benefit from capecitabine appears to be in the timing of recurrence, with patients on capecitabine experiencing recurrence on average later than those on observation, and hence giving an overall survival advantage in terms of both recurrence-free and overall survival, particularly in the first 2 years post-randomisation.

The BILCAP trial included all anatomical subgroups of cholangiocarcinoma (and gallbladder cancer) accepting that they have clinical and molecular differences. [11] This was a pragmatic approach which made the trial feasible to perform. This does give the opportunity to compare the outcome for different anatomical sites following surgery, with and without capecitabine. The overall survival curves for the 4 disease sites (figure 2) are similar with overlapping 95% confidence intervals although numerically patients GBC appear to have a survival advantage. This may however be influenced by the number of patients with incidental GBC (Table 1) in this subgroup. The survival analysis expressed in hazard ratios shown in table 2 and corrected for other factors gives a more useful description. In this model patients with iCCA have a numerically worse outlook compared to the comparator (pCCA) and those with dCCA or GBC. However, there is no clear or statistically significant difference between the disease sites and the trial is not adequately powered to show such.

The recent advances in the management of advanced biliary tract cancer have been in the targeted therapy of actionable alterations including FGFR, IDH1 and BRAF amongst others. [12-14]Understanding the absolute benefit of targeted agents has been hampered by the limited knowledge of the natural history of each subgroup and whether the targeted alterations are also prognostic as well as predictive. The molecular description of the BILCAP study (currently underway) may provide further insights into the biology of individual subgroups as well as other prognostic variables such as the R status. Even in this large study, this analysis will be limited by the numbers of patients in each subgroup emphasising the importance of cross study collaboration.

The follow-up of patients following potentially-curative resection of a BTC has hitherto been somewhat arbitrary, based mostly on local preference and resource. The long-term BILCAP data suggest a pattern of recurrence that will inform a follow-up program. The possibility of recurrence is still present even at 5 years and recurrence occasionally develops thereafter. This suggests that follow up with appropriate imaging should continue at least until 5 years. Although the benefit of imaging over symptomatic surveillance is unlikely ever to be formally demonstrated, the establishment of 1st-and 2nd-line standard-of-care chemotherapy[9,15] and the potential of benefit from targeted therapies in selected sub-groups[12-14] would argue for active rather than symptomatic surveillance.

In summary, the benefit of adjuvant capecitabine following curative resection of biliary tract cancers has been maintained with a longer-term analysis of the data. The need to continue clinical trial activity, in particular the continued collection of material for translational analysis, is critical.

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