Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study

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Summary

Background **Patients with biliary tract cancer have a poor prognosis, and, until recently, no standard palliative chemotherapy has been defined. We aimed to investigate the efficacy and safety of cetuximab in combination with gemcitabine and oxaliplatin (GEMOX) for first-line treatment of biliary tract cancer.**

Methods **From Oct 1, 2006, to July 26, 2008, patients with unresectable locally advanced or metastatic biliary tract cancer were sequentially enrolled and treated at one centre in Austria. All patients received intravenous infusions of 500 mg/m² cetuximab on day 1, 1000 mg/m² gemcitabine on day 1, and 100 mg/m² oxaliplatin on day 2, every 2 weeks for 12 cycles. The primary outcome was overall response rate. Analysis was by intention to treat. Adverse reactions were assessed according to National Cancer Institute Common Toxicity Criteria. The study is completed and registered with ClinicalTrials.gov, number NCT01216345.**

Findings **30 patients with median age of 68 years (IQR 62–73) were enrolled and included in the analysis. Objective response occurred in 19 patients (63%; 95% CI 56·2–69·8), of whom three (10%; 3·2–16·8) achieved complete response, and 16 (53%; 46·2–59·8) achieved partial response. Nine patients underwent potentially curative secondary resection after major response to therapy. Grade 3 adverse events were recorded in 13 patients: skin rash (n=4), peripheral neuropathy (n=4), thrombocytopenia (n=3), nausea (n=1), diarrhoea (n=1), and neutropenia (n=1); no grade 4 adverse events were recorded.**

Interpretation **Cetuximab plus GEMOX was well tolerated and had encouraging antitumour activity, leading to secondary resection in a third of patients. These findings warrant further study of cetuximab plus GEMOX in a large randomised trial.**

Funding **Association of Research on the Biology of Liver Tumors, Vienna, Austria.**

Introduction

Biliary tract carcinomas, comprising intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer, are relatively rare tumours, although their incidence is increasing worldwide, accounting for 3% of all gastrointestinal tumours.[1,2] Although risk factors for development of cholangiocarcinoma include chronic biliary inflammation, cholestasis, or congenital abnormalities, most cases of cholangiocarcinoma, especially the intrahepatic variant, do not have these classic risk factors.[3] The non-specific symptoms of cholangiocarcinoma mean that more than 75% of cases are unresectable because of the advanced stage of disease at diagnosis. The only curative treatment is surgical resection,[4] but, even after surgical resection, recurrence is frequently reported. Therefore, prognosis is poor and overall survival, including cases after resection, is less than 15% at 5 years.[5]

Patients with locally advanced or metastatic biliary tract cancer can be considered for palliative chemotherapy. More than 120 chemotherapy trials have been published since 1985, but most of these are non-randomised phase 2 studies with small sample sizes. Findings from Valle and colleagues' randomised phase 3 trial,[6] which was extended from a randomised phase 2 trial, will certainly affect first-line palliative care in this setting. Addition of cisplatin to standard treatment with gemcitabine significantly improved progression-free survival (8·5 *vs* 6·5 months; log-rank test p=0·003) and overall survival (11·7 *vs* 8·2 months; p=0·002) compared with gemcitabine alone.[6] Gemcitabine, a purine antimetabolite, has promising activity against biliary tract cancer, with a response rate of up to 35% when used alone.[7,8] Furthermore, gemcitabine has antitumour activity when used in combination with other agents, such as cisplatin or oxaliplatin, and seems to be well tolerated.[9,10] Nevertheless, new treatment combinations are urgently needed to increase response rates, especially to extend survival by removal of tumour remnants after liver resection.

Cetuximab is a targeted therapy directed against the epithelial growth factor receptor (EGFR), which has been associated with improved outcome in various malignancies, including colorectal, lung, and head and neck cancer.[11–13] Findings of in-vitro studies have shown that EGFR is activated by bile acids, leading to cyclo-oxygenase-2 (COX-2) expression via the mitogen-activated protein kinase

signalling cascade, and induction of COX-2 expression has been implicated in the genesis and progression of bile duct cancer.[14] Mutations in the *KRAS* gene are associated with inactivity of cetuximab in the treatment of metastatic colorectal cancer.[12,15] *KRAS* encodes a small G-protein which acts downstream of EGFR and is an essential component of the ligand-dependent EGFR signalling pathway. *KRAS* mutations, often occurring at codons 12 and 13, lead to constitutive activation of the protein and associated signalling.[16] So far, few reports are available on the role of *KRAS* mutation status in cholangiocarcinoma.[17] In a small study by Paule and colleagues,[18] nine patients with advanced intrahepatic cholangiocarcinoma who were resistant to gemcitabine and oxaliplatin (GEMOX), received cetuximab with GEMOX. This combination seemed to be well tolerated and showed activity in these patients,[18] however, no information was reported about *KRAS* mutation status of tumours. Furthermore, Roach and colleagues[19] presented first results of a combination of irinotecan, oxaliplatin, and cetuximab in metastatic pancreatic cancer with impressive response rates.

In this prospective single-centre phase 2 study, we aimed to investigate the therapeutic efficacy and safety of cetuximab in combination with GEMOX for palliative first-line treatment of patients with cholangiocarcinoma, and to study the relevance of the *KRAS* mutation status of the tumour.

Methods

Patients

Patients were sequentially enrolled from one centre in Austria and treated between Oct 1, 2006, and July 26, 2008. Patients were eligible for inclusion in the study if they met the following inclusion criteria: advanced or metastatic biliary tract cancer, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer, proven to be unresectable on histological or cytological assessment; 18 years or older; Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower; bidimensionally measurable disease (at least one index lesion capable of two dimensional measurement by CT scan or MRI); no previous chemotherapy for advanced disease; adequate bone marrow reserve (neutrophil count >1500 cells per µL, platelet count >100 000 per µL); adequate renal function (serum creatinine ≤1·5 times the upper limit of normal); and adequate hepatic function (serum bilirubin <2·5 times the upper limit of normal, serum aminotransferase ≤5 times the upper limit of normal). Patients with obstructive jaundice had to achieve bilirubin concentration of lower than 34·2 µmol/L by placement of a biliary stent before study treatment was started.

Patients were excluded if they had mixed hepatocellular carcinoma and cholangiocarcinoma, resectable disease, brain metastases, serious or uncontrolled concurrent medical illness, or history of other malignancies (with the exception of excised cervical or basal skin or squamous-cell carcinoma), and peripheral neuropathy (grade >1). Patients who had received palliative treatment previously, or who were pregnant or nursing were also excluded. Intrahepatic cholangiocarcinoma was defined as unresectable if resection would not preserve sufficient functional liver (30% of the total liver volume) with adequate vascular inflow and hepatic venous outflow. Extrahepatic cholangiocarcinoma was defined as unresectable by involvement of adjacent organs and vascular structures.

Before enrolment began, this trial was approved by the institutional review board. All patients gave written informed consent according to institutional guidelines before study entry.

Procedures

Patients received 500 mg/m² cetuximab as a 2-h intravenous infusion on day 1. Patients were then observed for 30 min for signs of anaphylaxis or other infusion-related reactions. In the absence of reactions, 1000 mg/m² gemcitabine was given as a 100-min intravenous infusion on day 1 (based on its increased activity relative to the bolus infusion[20]), followed by 100 mg/m² oxaliplatin as a 2-h intravenous infusion on day 2.[21] Treatment courses were repeated every 2 weeks for a total of 12 cycles, unless there was evidence of resectable or progressive disease or unacceptable toxicity. Prophylactic, antiemetic drugs routinely given before the study drugs included 8 mg ondansetron and 8 mg dexamethasone. Topical or oral antibiotics, or both, were also given in cases of skin toxicity.

Adverse reactions were assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 3.0) at every cycle. If patients had a haematological adverse event of grade 4, or a non-haematological adverse event of grade 3 or higher, the dose of chemotherapeutic drug was reduced by 25% for all subsequent doses. Additionally, for persistent severe neurotoxicity, despite a 25% dose reduction, oxaliplatin was temporarily withdrawn and therapy with cetuximab and gemcitabine was continued until recovery. In patients who developed allergic reactions or laryngeal spasm syndrome, the duration of the oxaliplatin infusion was increased to 4–6 h. If an allergic reaction occurred despite extension of infusion time, oxaliplatin was discontinued. In the event of discontinuation of oxaliplatin for any toxic event, cetuximab and gemcitabine could be continued at the same dose and schedule. Treatment was delayed for up to 2 weeks if the absolute neutrophil count was lower than 1500 cells per µL or the platelet count was lower than 100 000 per µL. If a patient had skin toxicity of grade 3, the subsequent dose of cetuximab was delayed for up to 2 weeks with no change in dose. If a patient had a second occurrence of skin toxicity of grade 3, cetuximab was again delayed for up to 2 weeks and the dose was then reduced by 25% for all subsequent doses. GEMOX was not withheld if the cetuximab infusion was suspended due to skin toxicity. Patients who needed more than 3 weeks recovery from an adverse reaction were excluded from the study.

	Patients (n=30)
ECOG performance status	
0	24
1	5
2	1
Previous therapy	
Curative surgery	11
Biliary stenting	4
Disease status	
Locally advanced	5
Metastatic	25
Tumour location and UICC stage*	
Intrahepatic cholangiocarcinoma	18
Stage IIIc	1
Stage IVb	17
Extrahepatic cholangiocarcinoma	9
Stage II	1
Stage III	3
Stage IV	5
Gallbladder cancer	3
Stage IV	3
Organs with metastases	
0	5
1	11
2	11
3	3
CA 19-9 (kU/L)	
Mean (SD)	640 (1983)
Median (IQR)	42 (9–116)

Data are number of patients, unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. UICC=Union for International Cancer Control. CA=carbohydrate antigen. *According to TNM classification of malignant tumours.[26]

Table 1: **Disease characteristics at baseline**

Assessment of patients before the start of study treatment included a complete medical history, physical examination, routine haematological and biochemical analyses, and CT or MRI scans of the thorax and abdomen to define the extent of disease. After this first assessment, complete blood (including platelet and differential) cell counts and serum biochemical analyses were obtained at least once per treatment cycle. Subjective symptoms, physical examination results, performance status, and all adverse reactions were recorded before each treatment cycle according to the NCI-CTC. Tumour response was assessed after four treatment cycles and every four cycles thereafter with the Response Evaluation Criteria in Solid Tumors (RECIST)[22] by CT or MRI scan; the assessment was confirmed by a radiologist who was masked to the protocol and study endpoint. Patients were discussed after every response measurement in a multidisciplinary team, comprising oncologists, liver surgeons, and radiologists, to assess further treatment strategies, including potential curative treatment options. Follow-up examinations included CT of the chest and abdomen and measurement of the tumour marker carbohydrate antigen 19-9 every 3 months during the first 2 years, and every 6 months thereafter. Patients were followed up until death.

To detect *KRAS* mutation, biopsy samples were obtained by fine-needle aspiration from all patients and used to create formalin-fixed paraffin-embedded tissue slides. Results from analysis of the slides were confirmed in resected specimens. Mutations in codons 12, 13, and 61 of the *KRAS* gene were detected by direct bidirectional sequencing of PCR products that were amplified from tumour DNA extracted from representative tumour tissue. Selected tumours were estimated to contain at least 70% tumour cells from haematoxylin and eosin staining of the slide. PCR primer sequences, cycling conditions, and annealing temperatures were used as described previously.[23] At the time of the pathological examination of our study material, the interaction between *BRAF* mutations and response to cetuximab was not widely known, therefore this analysis was not done.

The primary endpoint of this study was the best overall response rate to cetuximab in combination with GEMOX. Secondary endpoints included the toxicity of this combination regimen, secondary resection rate, progression-free survival, overall survival, *KRAS* mutation status, and the association between *KRAS* mutation and tumour response. Progression-free survival was defined as time from the first cycle to disease progression or death, whichever occurred first. Overall survival was defined as the time from the first cycle to death.

Statistical analysis

When we designed our trial, only one report had been published on combination treatment with gemcitabine and oxaliplatin.[24] From all trials of chemotherapy for biliary tract cancer published during 1985–2006, the pooled response rate was 22·6%. Simon's statistics[25] were used to calculate the sample size needed to verify a sufficient response to the regimen. In a two-stage design with an unacceptable response probability of 20%, an acceptable response probability of 40%, and 80% power, 30 patients needed to be enrolled and treated. Efficacy and safety analyses were done in all patients who received at least one dose of the study drug. All tests were two-sided and p values of less than 0·05 were judged to be significant. The Kaplan-Meier method was used to estimate overall and progression-free survival. Statistical analyses were done with SPSS (version 17.0).

The study is completed and registered with ClinicalTrials.gov, number NCT01216345.

Role of the funding source

The trial sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data and had final responsibility to submit for publication.

	Grade 1–2	Grade 3
Skin toxicity	24	4
Peripheral neuropathy	21	4
Nausea	17	1
Diarrhoea	8	1
Anaemia	25	0
Neutropenia	8	1
Thrombocytopenia	10	3

30 patients had grade 1–2 adverse events and 13 patients had grade 3 adverse events. Patients who had more than one type of adverse event have been listed against all relevant types of events, but patients who had more than one occurrence of the same type of event are recorded only once.

Table 2: **Adverse events**

	Patients (n=30)
Response	
Complete response	3 (10%; 3·2–16·8)
Partial response	16 (53%; 46·2–59·8)
Stable disease	5 (17%; 10·2–23·8)
Progressive disease	6 (20%; 13·2–26·8)
Overall response rate	19 (63%; 56·2–69·8)
Disease control rate	24 (80%; 73·2–86·8)

Data are number (%; 95% CI).

Table 3: **Response to treatment**

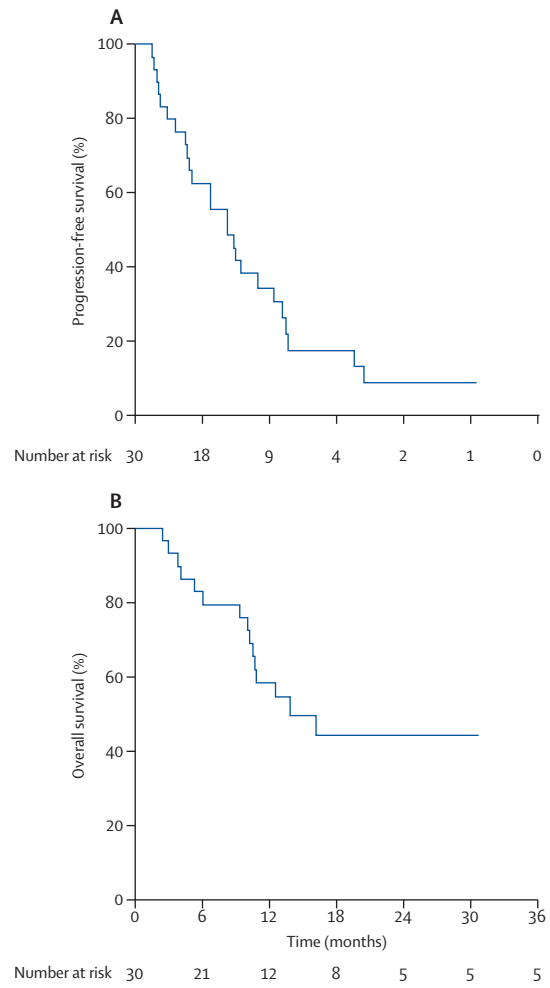

Figure 1: **Kaplan-Meier plot of progression-free survival (A) and overall survival (B) for all patients**

Results

30 patients, 15 men and 15 women, with a median age of 68 years (IQR 62–73) were enrolled. Most patients had ECOG performance status 0, and a large proportion had intrahepatic cholangiocarcinoma, with fewer diagnosed with extrahepatic cholangiocarcinoma or gallbladder cancer (table 1).

All patients received at least two cycles of cetuximab plus GEMOX, with a median of 7·5 cycles (range 2·0–12·0). 17 patients received the full scheduled dose of chemotherapy before the end of planned treatment, progression of disease, or secondary surgical resection. Of the remaining 13 patients, nine had a 25% reduction in the dose of oxaliplatin, one had a 25% reduction in the dose of cetuximab, two had a 25% reduction in the dose of GEMOX, and one discontinued oxaliplatin because of a hypersensitivity reaction during cycle four.

Cetuximab was quite well tolerated: no patient discontinued treatment because of toxic effects, and no treatment-related deaths were recorded. During the study, grade 3 drug-related adverse events occurred in 13 patients, and no grade 4 adverse events were reported (table 2). Nearly all patients developed cetuximab-related acneiform rash: two of grade 0; 14 of grade 1; ten of grade 2; and four of grade 3.

Tumour response was assessed in all 30 patients. An objective response was recorded in 19 patients (63%; 95% CI 56·2–69·8), with a higher proportion achieving radiologically confirmed partial response than complete response (table 3). The remaining patients had either stable or progressive disease. The overall disease control rate was 80% (table 3).

Nine patients (30%) underwent secondary curative resection after major response to therapy. Five of these patients had intrahepatic cholangiocarcinoma that was initially not amenable to secondary resection, and four presented with locally advanced extrahepatic tumours which were unresectable because of vascular involvement. In eight of the nine patients, cetuximab plus GEMOX resulted in major tumour shrinkage by at least 40% of the sum of the longest diameter of target lesions; one patient had a reduction of 25% and was therefore rated as stable disease. Major liver resection (removal of three or more segments) was done to achieve potential cure in all nine patients. Additionally, one patient underwent a combined surgical and thermo-ablative procedure. Furthermore, two patients underwent surgical

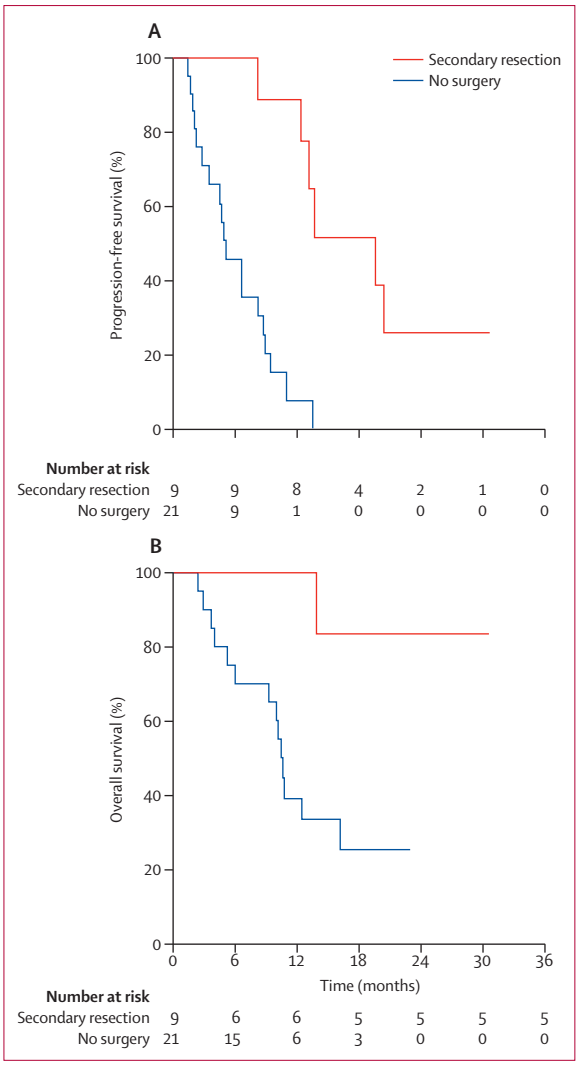

Figure 2: **Kaplan-Meier plot of progression-free survival (A) and overall survival (B) by resection status**

exploration: in both patients, secondary resection was abandoned because of peritoneal disease which was not detected during preoperative staging.

Median follow-up in all 30 patients was 22·0 months (95% CI 12·5–31·1). Median progression-free survival of all treated patients was 8·8 months (95% CI 5·1–12·5; figure 1A). For the nine patients who underwent secondary resection, median progression-free survival was 21·2 months (12·5–29·8) versus 6·8 months (4·5–9·1) in those who did not have surgery (log-rank test p=0·0001; figure 2A). Median overall survival of all treated patients was 15·2 months (9·9–20·5; figure 1B). Median overall survival was not reached in patients who underwent secondary resection, and was 11·6 months (10·9–12·3) in those ineligible for secondary surgery (figure 2B).

27 patients (90%) had tumours that were wildtype for *KRAS*, with *KRAS* mutations recorded in only three patients' tumours (10%). Of these three patients, one had extrahepatic cholangiocarcinoma, and two had an intrahepatic cholangiocarcinoma. All three patients did not progress under treatment: two had a partial response, and one had stable disease. One of the patients with partial response was able to have liver resection after four cycles of combination therapy.

A significant positive correlation was identified between the grade of acneiform rash that developed during treatment and the response achieved (p=0·01). All patients who developed a skin rash of grade 2 or 3 had either a radiological complete response or a partial response, one patient with stable disease had grade 2 rash, and all patients with progressive disease had no rash or grade 1 rash.

Discussion

In our study of patients with unresectable biliary tract cancer, we recorded a high overall response rate and good disease control after treatment with cetuximab and GEMOX (panel). This combination treatment had an acceptable toxicity profile and resulted in potentially curative secondary resection in a third of patients, which significantly lengthened progression-free survival. These findings provide justification for further studies of this treatment combination in a randomised study of a large cohort.

Cholangiocarcinoma is an orphan disease.[27] The overall prognosis of the disease is poor and no standardised treatment regimen has been established. Experienced cancer centres around the world have reported an increasing number of referrals of patients with cholangiocarcinomas.[28,29] In their pooled analysis, Eckel and Schmid[30] suggested that combination therapy with gemcitabine plus a platinum compound should be the palliative regimen backbone until new data become available. The increasing number of patients with cholangiocarcinoma, especially the intrahepatic variant, prompted us to design a study to show improved response rates in patients with unresectable disease.[4] Furthermore the overall benefit of secondary surgery in this setting has not been assessed until now, so an improved response rate might be expected to be associated with lengthening of progression-free and overall survival.

On the basis of promising results from the addition of cetuximab to standard combination chemotherapy in other solid tumours, we selected this EGFR antibody to boost the response rate of our standard combination regimen for cholangiocarcinomas. In view of the substantially increased secondary resection rate after first-line treatment with cetuximab in metastatic colorectal cancer,[31] we included this approach as a secondary endpoint. In this study, addition of cetuximab to GEMOX was associated with encouraging antitumour activity, with an overall response rate of 63% and stable disease recorded in half of remaining patients, leading to a disease control rate of 80%. Comparison of these results with response rates achieved in other studies verifies that cetuximab plus GEMOX has better overall response rate than does

gemcitabine alone, GEMOX alone, or other chemotherapy combinations, although cross-study comparison has limitations.[32–34] Although progression-free and overall survival were promising in the recently published ABC-02 trial,[6] response rates were only marginally improved by combination therapy and remained below 30% in both treatment groups. In an interim analysis of a multicentre, randomised phase 2 trial of GEMOX with or without cetuximab in 101 patients, Malka and colleagues[35] showed a progression-free survival benefit after 4 months (the primary endpoint) in 36 patients on GEMOX plus cetuximab (61%) compared with GEMOX alone (44%). Response rates were less impressive, with partial responses in only three patients receiving GEMOX and two receiving GEMOX plus cetuximab. Full data analysis will hopefully clarify this discrepancy.

In metastatic colorectal cancer, improved response rates in unresectable disease are needed for potentially curative secondary surgery to be possible, and this multidisciplinary strategy has doubled overall survival.[36] Further to the high overall response rate achieved with combined GEMOX and cetuximab in our study, we were able to show an impressive secondary curative resection rate of 30%. We have to point out, however, that median progression-free and overall survival of all 30 patients in our trial were similar to those reported in the ABC-02 trial,[6] and therefore GEMOX with or without cetuximab needs to be studied in a randomised trial. Although median overall survival is not yet available for patients who had secondary surgery, median progression-free survival was three times higher in patients who had secondary surgery than in those who did not, providing confidence for similar estimates for median overall survival.

Data from studies investigating other targeted agents in cholangiocarcinoma are scarce and have rarely reported improved response rates.[37,38] In a review of molecular targeted therapies, Wiedmann and Mössner[39] reported that combination of chemotherapy with cetuximab or bevacizumab can improve response rates, but the improvement reported with addition of bevacizumab was marginal (45%) compared with that reported with addition of cetuximab in our study (63%). Furthermore, none of the studies of accessible palliative therapies has so far reported rates of secondary resection.

Following on from findings in metastatic colorectal cancer, we investigated the association between *KRAS* mutation status in cholangiocarcinoma and response to cetuximab. *KRAS* mutations were detected in few patients and did not preclude benefit from combined cetuximab and GEMOX. In a study of *KRAS* mutations in codon 12, Malats and colleagues[17] reported an overall prevalence of 41% (31/76) in patients with extrahepatic bile duct cancer, 34% (15/44) in gallbladder cancers, 50% (10/20) in extrahepatic bile duct cancers, and 50% (3/6) in ampullary cancers. Patients with *KRAS*-mutated tumours had a shorter median survival time than did those with wildtype tumours (1·67 *vs* 7·67 months; p=0·071). Additional information in published reports suggests that the percentage of *KRAS* mutations is dependent on cholangiocarcinoma location.[40–42] Clearly the role of *KRAS* mutation in cholangiocarcinoma tumorigenesis and response to treatment with cetuximab needs further analysis in large cohorts before recommendations can be made on its predictive or prognostic value in this setting. Since our trial is not randomised, has a small sample size, and is single centre, we await further confirmation of our findings in a study that overcomes these weaknesses.

Panel: Research in context

Systemic review

We searched PubMed for articles with the search terms "biliary tract cancer", "unresectable", "advanced", "metastatic", and "systemic chemotherapy". At the time recruitment began, no published randomised trial had addressed the potential benefit of an inhibitor of the epithelial growth factor receptor in addition to combination chemotherapy. The trial was designed on the basis that such treatment was associated with a response benefit in refractory cholangiocarcinoma[18] and pancreatic cancer,[19] and with an increased rate of secondary resection in metastatic colorectal cancer.

Interpretation

We have shown that addition of cetuximab to gemcitabine and oxaliplatin in treatment of biliary tract cancer is associated with increased response, substantial tumour shrinkage, and the potential for secondary resection. The results of this multidisciplinary approach support the presentation of patients with biliary tract cancer at multidisciplinary team meetings at diagnosis to discuss the treatment aim and assess the best therapeutic strategy for each patient.

Contributors

BG, DT, and TG designed the study. BG, JS, UH, DT, KK, RR, SF-P, and TG collected data. BG, JS, FW, DT, and TG analysed and interpreted the data. BG, JS, DT, and TG wrote the report. All authors had full access to the final version of the report and agreed to the submission.

Conflicts of interest

BG has received payment for lectures from Roche and Merck Serono; provided an advisory role for Roche and Gruenenthal; received research funding from Bayer; and has received travel and accommodation expenses from Roche. UH has received payment for lectures from Sandoz and Merck Serono; and UH and UH's institution have received travel expenses from Sanofi-Aventis, Sandoz, Amgen, and Merck Serono. SF has received travel expenses from Roche and Astra Zeneca. TG has received payment for lectures from Roche, Pfizer, Sanofi-Aventis, Merck Serono, Amgen, and Bayer; provided an advisory role for Roche, Pfizer, and Bayer; received research funding from Roche, Pfizer, Sanofi-Aventis, Merck Serono, and Amgen; and received payment for development of educational presentations from Roche and Merck Serono. TG's institution has received research funding from Bayer; and travel and accommodation expenses from Roche and Merck Serono. BG, DT, and TG are members of the Association of Research on the Biology of Liver Tumors. All other authors declared no conflicts of interest.

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45th Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, USA (2009); at the 10th World Congress on Gastrointestinal Cancer, Barcelona, Spain (2008); and at the 50th Annual Meeting of the Austrian Society of Surgery, Vienna, Austria (2009).

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