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LETTER TO THE EDITOR

Gemcitabine, capecitabine and oxaliplatin with or without cetuximab in advanced biliary tract carcinoma

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Biliary tract carcinoma includes gallbladder cancer and cholangiocarcinoma. Cholangiocarcinoma can be subdivided into intrahepatic, hilar (perihilar, Klatskin) and extrahepatic carcinoma. Biliary tract carcinoma is a relative rare cancer which account for less than 1% of new cancer cases. Only resection is a curative treatment, but unfortunately resection is only possible in approximately 10%, leaving most patients with advanced disease. For patients with advanced disease only palliative treatment is possible. The most active drugs in phase 2 trials are gemcitabine [1,2] flouropyrimidine/capecitabine [3,4] and cisplatin/oxaliplatin [5–9]. Support for gemcitabine as an anchor drug for the treatment of advanced biliary tract carcinoma comes from a pooled analysis of 104 trials showing that the subgroup who received a combination of gemcitabine and a platinium-based agent had the greatest benefit [10]. In 2010 Valle et al. published a study with 410 patients comparing cisplatin and gemcitabine to gemcitabine alone [11]. The patients who received cisplatin and gemcitabine had a better median overall survival (OS) of 11.7 months versus 8.1 months with gemcitabine monotherapy. Cisplatin and gemcitabine were therefore suggested as standard treatment to patients with advanced biliary tract carcinoma. One small phase 2 trial randomized between best supportive care, 5-FU monotherapy and gemcitabine plus oxaliplatin and found the gemcitabine plus oxaliplatin combination superior to 5-FU alone [12]. Several phase 2 trials have replaced cisplatin with oxaliplatin and the combination of gemcitabine and oxaliplatin showed similar OS of approximately 12 months [12,13]. A systematic review of cisplatin/gemcitabine and oxaliplatin/gemcitabine found no difference between the two regimens [14]. The triplet of gemcitabine, oxaliplatin and capecitabine has been examined in a small phase 2 trial and in a large retrospective analysis [15,16]. In the triplet regime a lower oxaliplatin dose was used compared to the double, which made it well tolerable and with similar OS as gemcitabine and platinium.

The epidermal growth factor receptor (EGFR) signaling pathway regulates biliary epithelial cell growth and proliferation, and EGFR is overexpressed in 67–100% of biliary carcinoma, making it a rational target for treatment [17]. Studies of *KRAS* in biliary tract carcinoma found few patients with mutations in *KRAS*, leaving 70–90% with wild-type [18–20], which further support the idea of adding an EGFR-inhibitor to the chemotherapy. Some smaller trials have shown encouraging results when adding cetuximab to chemotherapy [21–24]. In the present study we wanted to investigate the efficiency of adding cetuximab to the triplet gemcitabine, capecitabine and oxaliplatin. To our knowledge, this is the first trial to establish the efficacy of the combination of capecitabine, oxaliplatin, gemcitabine and cetuximab in biliary tract carcinoma.

Material and methods

Design

This is a prospective phase 2 trial planned to include 50 patients with biliary tract carcinoma to receive capecitabine, gemcitabine, oxaliplatin and cetuximab. The inclusion period was from January 2011 to August 2013 at one institution. The primary end point was median progression-free survival (PFS) and the secondary end points were OS, response rate, rate converted to resection and toxicity. In the same period 57 similar patients received the same treatment but without cetuximab. The reason for not being in the trial was: they were never asked to participate, they did not want to, or the CT scan was too old for inclusion. This group was used as a control group. Only patients with a good performance status (PS) 0 or 1 in ECOG performance score were included as an earlier trial by the Danish group have shown very poor survival for patients with PS 2 [16]. All patients were treated regardless of *RAS* or *BRAF* status. Retrospectively *KRAS, NRAS* and *BRAF* were tested with next generation sequencing.

Patients and treatment

Patients over 18 years were included if they had a histo- or cytological diagnosis of non-resectable or recurrent biliary tract carcinoma. In cases with indeterminate but malignant histology, imaging should support the diagnosis and other primary tumors should be excluded. Location of the primary tumor could be intrahepatic, hilar or extrahepatic bile ducts or in the

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gallbladder (ampulla of Vater was not included). All patients were evaluated as non-resectable by liver surgeons. Patients in performance status 0 or 1 were included if they had a bilirubin less than two times the upper limit of the normal range and adequate renal and bone marrow functions. Patients were excluded if they had received previous palliative chemotherapy for biliary tract carcinoma, clinical significant comorbidities, active uncontrolled infection or had additional malignancy within the past five years (except carcinoma in situ in cervix or non-melanoma skin cancer). All patients gave written consent and the protocol was approved by the ethics and national board committees. The protocol was registered with ClinicalTrials.gov number NCT-01247337.

Assessment of patients before start of study included complete medical history, physical examination, routine hematological and biochemical analyses. CT scan of thorax and abdomen should be performed within the last 28 days. Adverse events were graded according to Common Terminology Criteria for Adverse events (NCI-CTCAE) version 3.1. Retrospectively the patients were tested for *KRAS* mutations in codon 1-189, *NRAS* in codon 1-189 and *BRAF* in codon 1-664 and 669-766 with next generation sequencing. The schedules used were capecitabine 650 mg/m^2 BID continuously with gemcitabine 1000 mg/m^2, oxaliplatin 50 mg/m^2 and cetuximab 500 mg/m^2 Day 1 in a two-week schedule. Oxaliplatin and gemcitabine were both given as an infusion over 30 minutes each. The first cetuximab infusion was given over two hours and the following infusions over one hour. The patients were pretreated with 100 mg prednisolone and 2 mg clemastin. In case of response the patient was reevaluated by liver surgeons. The patients continued treatment until progression. If a patient had toxicity to one drug this drug was reduced in dose or stopped while the other drugs were continued unchanged. CT scan was made every eight weeks. If treatment was stopped before progression on a CT scan, due to toxicity, the patient's own will or due to poor performance status, the patients were followed clinically until death. Fifty-seven similar patients, who received the same regimen but without cetuximab, were used as a control group,

Statistical analysis

All patients planned to receive chemotherapy were included. OS was calculated from the date of first treatment until the date of death. PFS was calculated from the date of first treatment until progression either on CT scan or clinical progression or death. OS and PFS were analyzed with the use of Kaplan-Meier curves calculated on IBM SPSS statistics version 19 (SPSS Inc., Chicago, IL, USA). Tumor response was evaluated with CT scan in accordance to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. The database was closed for analysis June 2015.

Results

Fifty-three patients were included in this phase 2 trial to receive capecitabine, gemcitabine, oxaliplatin with cetuximab. Fifty-seven patients, who received the same chemotherapy but without cetuximab, were used as a control group. Patients' characteristics are listed in Table I. The majority of the patients were in performance status 0. There was a slight female preponderance (60%), and most tumors were located intrahepatic. We found a PFS of 8.5 months and OS of 12.8 months in the cetuximab group compared to a PFS of 8.1 months and OS of 12.4 months in the control group (Table II). The response rate was also similar in the two groups (23% and 26%, respectively). Only seven patients (three in the experimental arm and four in the control arm) were converted to resection on CT scan and had an explorative laparotomy. Five of the seven patients were resectable. Of the five resected patients

Table I. Patient characteristics in our study with capecitabine, gemcitabine, oxaliplatin and cetuximab compared to a control group without cetuximab.

	Capecitabine + gemcitabine + oxaliplatin + cetuximab (N=53)	Capecitabine + gemcitabine + oxaliplatin (N=57)
Median age, year	64.9	63.9
Sex, no. (%)		
Female	32 (60%)	29 (51%)
Male	21 (40%)	28 (49%)
ECOG performance status score, no. (%)		
0	34 (64%)	37 (65%)
1	19 (36%)	20 (35%)
Primary tumor site, no. (%)		
Gallbladder	13 (25%)	11 (19%)
Intrahepatic	24 (45%)	32 (57%)
Hilar	9 (17%)	9 (16%)
Extrahepatic	7 (13%)	5 (9%)
RAS and BRAF mutations in 29 patients:		
KRAS	6 (20%)	NA
NRAS	0	
BRAF	1 (3%)	
Previous treatments		
Curative-intent surgery	5 non-radical	2 non-radical
Treated with chemo-radiotherapy	1	2
Curative surgery with later relapse	4 radical	2 radical
Treated with adjuvant gemcitabine	1	1
Primary biliary stenting	10 (19%)	15 (26%)
Number of treatments	15 (1–46)	14 (1–36)

Table II. Median PFS, median OS, response rate, rate converted to resection, 1-year and 2-year survival from patients with biliary tract carcinoma treated with capecitabine, gemcitabine and oxaliplatin with or without cetuximab.

	Capecitabine + gemcitabine + oxaliplatin + cetuximab (N=53)	Capecitabine + gemcitabine oxaliplatin (N=57)
PFS (months)	8.5 (7.3–9.7)	8.1 (5.9–10.4)
OS (months)	12.8 (8.8–16.9)	12.4 (9.4–15.5)
Response rate (%)		
Complete response	1 (2%)	0
Partial response	11 (21%)	15 (26%)
Stable disease	31 (58%)	23 (40%)
Progressive disease	6 (11%)	4 (7%)
Non-evaluable[a]	4 (7%)	15 (26%)
Number converted to resection on CT scan	3[b]	4[c]
1 year survival (%)	27 (51%)	30 (53%)
2 year survival (%)	9 (17%)	15 (28%)

[a]Non-evaluable were patients without measurable disease or patients who never had a second CT scan;
[b]3 patients had explorative laparotomy but only 1 was resectable and had later relapse;
[c]4 patients were resectable, 3 had relapse.

Table III. Grade 3 to 4 toxicity.

	Capecitabine + gemcitabine + oxaliplatin + cetuximab (N=53)	Capecitabine + gemcitabine + oxaliplatin (N=57)
Palmar-plantar-erythema	6 (11%)	6 (11%)
Neuropathy	6 (11%)	5 (9%)
Neutropenia	2 (4%)	1 (2%)
Fatigue	8 (15%)	10 (18%)
Nausea	3 (6%)	2 (4%)
Vomiting	2 (4%)	2 (4%)
Diarrhea	0	1 (2%)
Elevated liver enzymes	21 (40%)	NA
Thromboembolic event	9 (17%)	NA
Allergic reaction to oxaliplatin	4 (8%)	NA
Skin toxicity to cetuximab	4 (8%)	-
Allergic reaction to cetuximab	4 (8%)	-

NA, not available.

four have relapsed. In subgroup analysis we found no difference in PFS or OS between sexes, tumor site or in age over or less than 65 years (data not shown). In 29 patients we obtained tissue specimens with sufficient DNA for *KRAS, NRAS* and *BRAF* mutation analysis. In six (20%) of the 29 patients we found a *KRAS* mutation, in none we found a *NRAS* mutation and in one (3%) we found a *BRAF* mutation. There was no statistical difference according to PFS or OS between wild-type and mutated.

The patients continued treatment until progression and had in average 15 treatments spanning from one to 46 in the cetuximab arm (Table I). In the control arm, they received 14 treatments in average spanning from one to 36. The treatment was well tolerated with few grade 3 or 4 adverse events (Table III). Four patients had an allergic reaction to oxaliplatin (after treatment 6, 7, 10 and 17, respectively) and stopped oxaliplatin for that reason. The rest stopped oxaliplatin after 12–18 treatments, due to neurotoxicity. Nearly no dose reduction of oxaliplatin was necessary. The patients tolerated gemcitabine well and only a few patients had palmar-plantar erythema due to capecitabine. Four patients had an allergic reaction to cetuximab and had to stop cetuximab treatment. All the patients had some skin toxicity to cetuximab but it was well managed. The relative high incident of thromboembolic events may be due to patients continuing treatment and registration until progression.

Discussion

Gemcitabine and platinium is considered standard treatment to biliary tract carcinoma. It has never been elucidated in a randomized trial whether cisplatin and oxaliplatin has similar activity. Most trials using oxaliplatin use doses from 85 mg/m^2 to 100 mg/m^2 every second week, while we have found similar efficacy with a lower oxaliplatin dose of 50 mg/m^2 every second week together with capecitabine. The lower oxaliplatin dose resulted in very limited problems with nausea and cold-induced neurotoxicity, while the cumulative neurotoxicity was similar to studies with higher dose oxaliplatin. All our patients received oxaliplatin for 6–9 months, except if the disease progressed before the six months or if they had an allergic reaction to oxaliplatin. The cumulative dose of oxaliplatin may therefore be equal to regimens with higher doses of oxaliplatin. Due to the low toxicity of this triple combination with similar OS as gemcitabine and platinium, we wanted to evaluate the effectiveness of adding cetuximab to gemcitabine, oxaliplatin and capecitabine in non-resectable biliary tract carcinoma. Some smaller trials have shown encouraging results when adding cetuximab to chemotherapy [21–24]. Along with this study two randomized trial with gemcitabine and oxaliplatin with or without cetuximab [18,19] have been published in 2014 and 2015. They showed no improvement in OS when cetuximab was added. Even in subgroup analysis for *RAS*- and *BRAF* wild-type there were no improvement in OS. Our study confirms the randomized trials with no improvement when adding cetuximab to capecitabine, oxaliplatin and gemcitabine. In a retrospective analysis testing for mutations with next generation sequencing we found 20% to have a mutation in *KRAS*, 0% in *NRAS* and 3% in *BRAF*. These results with few mutations are in accordance with earlier studies [18–20]. We found no significant difference in PFS or OS between wild-type and mutated but the numbers were too small to make any conclusion.

In conclusion, adding cetuximab to gemcitabine, capecitabine and oxaliplatin is well tolerated but does not improve PFS or OS. Therefore adding cetuximab to capecitabine, oxaliplatin and gemcitabine to patients with biliary tract carcinoma cannot be recommended.

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