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Phase II marker-driven trial of panitumumab and chemotherapy in *KRAS* wild-type biliary tract cancer

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Background: Combination chemotherapy has proven beneficial in biliary tract cancer and further improvements may be achieved by individualizing treatment based on biomarkers and by adding biological agents. We report the effect of chemotherapy with panitumumab as first-line therapy for *KRAS* wild-type irresectable biliary tract cancer.
Patients and methods: Patients were treated with gemcitabine 1000 mg/m^2, oxaliplatin 60 mg/m^2, and panitumumab 6 mg/kg i.v. every 2 weeks followed by two daily administrations of capecitabine 1000 mg/m^2 in 7 days.
Results: During 22 months, 46 patients were included in a single institution. The primary end point, fraction of progression-free survival (PFS) at 6 months, was 31/42 [74%; 95% confidence interval (CI) 58% to 84%]. Forty-two patients had measurable disease. Response rate was 33% and disease control rate 86%. Median PFS was 8.3 months (95% CI 6.7–8.7 months) and median overall survival was 10.0 months (95% CI 7.4–12.7 months). Toxicity was manageable including eight cases of epidermal growth factor receptor-related skin adverse events of grade 2 or more.
Conclusions: Marker-driven patient selection is feasible in the systemic treatment of biliary tract cancer. Combination chemotherapy with panitumumab in patients with *KRAS* wild-type tumors met the efficacy criteria for future testing in a randomized trial.
Key words: biliary tract cancer, chemotherapy, cholangiocarcinoma, *KRAS*, marker-driven treatment, panitumumab

introduction

Biliary tract cancers or cholangiocarcinomas are malignant tumors arising anywhere in the mucosa lining the biliary tract. Anatomically, they are divided into intrahepatic, perihilar, or extrahepatic tumors and include Klatskin's tumors and gall bladder cancer [1]. The annual incidence is up to 1/100 000 in Western countries but much higher in other parts of the World [2]. The only curative treatment is radical resection, but only a small fraction of the patients have resectable disease at presentation. Furthermore, most patients undergoing resection will eventually relapse. Thus, there is a need for systemic treatment.

Regimens combining platinum and gemcitabine are considered as a standard chemotherapy in nonresectable patients [3, 4]. In Denmark, a combination of gemcitabine, oxaliplatin, and capecitabine has been evaluated in phase I and phase II trials [5]. Based on experience with other gastrointestinal tumors, additional effect may be expected when combining chemotherapy and epidermal growth factor receptor (EGFR) antibodies [6, 7].

The literature on EGFR inhibition in biliary tract cancer is sparse. The EGFR is overexpressed in a fraction of biliary tract cancer [8] and it may be targeted [9]. There are casuistic reports on the effect of the EGFR antibody cetuximab [10–13] and in a small study by Paule et al. [14], cetuximab reverted chemoresistance in two of nine patients. Besides cetuximab, one other EGFR antibody has been approved, panitumumab. Panitumumab is a fully humanized antibody targeting the extracellular domain of the EGFR [15]. Specific antineoplastic effect in colorectal cancer seems to depend on normal function of the signaling protein KRAS in the EGFR pathway as responses are only seen in *KRAS* wild-type (wt) tumors and not in tumors with self-activating mutations [16].

The purpose of this phase II trial was through a marker-driven approach to investigate the efficacy of combination chemotherapy and the EGFR inhibitor panitumumab in *KRAS* wild-type biliary tract cancer.

methods

eligibility criteria

Eligible patients were at least 18 years of age with a performance status of zero to two and irresectable biliary tract cancer defined as either histologically definitive diagnosis or malignant cells consistent with biliary tract cancer and simultaneous radiologically evident findings without curative options. The *KRAS* gene in tumor-derived DNA was assessed for seven mutations in codons 12 and 13 by a predeveloped kit (DxS Ltd, Manchester, UK) and quantitative PCR (ABI7900HT; Applied Biosystems, Foster City, CA) and only wild type was included. The patients had to have

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evaluable disease, i.e. the disease need not be measurable, adequate bone marrow, and renal function. Hyperbilirubinemia was allowed up to three times the upper limit of normal and alanine transaminase up to five times the upper limit of normal. Chemotherapy, radiotherapy, or immunotherapy was allowed only as (neo-)adjuvant therapy and not within 4 weeks before inclusion. Ineligibility criteria included pregnancy or breast feeding, serious concomitant medical illness, other serious malignancy within 5 years, neuropathy of grade 2 or more, known hypersensitivity to any of the active or auxiliary substances, or pulmonary pneumonitis.

The study was approved by the regional ethical committee and was conducted in accordance with the Declaration of Helsinki. The patients received oral and written information and were offered at least 1 day for reflection before giving a written informed consent. The trial was registered at ClinicalTrials.gov with the identifier NCT00779454.

study design and treatment

The study was an open-label phase II trial. It was run in parallel with a phase II study for patients with *KRAS*-mutated tumors receiving combination chemotherapy alone. This parallel trial is ongoing and results will be reported later.

Eligible patients were allocated to panitumumab 6 mg/kg, gemcitabine 1000 mg/m^2, and oxaliplatin 60 mg/m^2 on day 1 i.v. plus capecitabine 1000 mg/m^2 b.i.d. day 1–7. Gemcitabine was given at standard infusion rate of 30 min. Treatment was repeated every 2 weeks until progression or unacceptable toxicity. One cycle was defined as two treatments and lasted thus 4 weeks. In the case of febrile neutropenia or thrombocytopenic severe bleeding, chemotherapy was reduced by 25%. Oxaliplatin was interrupted, reduced to 75%, or discontinued in the event of neuropathy, as described in the summary of product characteristics. Capecitabine was interrupted, reduced, or discontinued in grade 2 or more hand and foot syndrome or gastrointestinal toxicity according to the summary of product characteristics. Panitumumab was on hold in grade 3 skin toxicity and continued at 50% when resolved. Skin moisturizers, topical steroids and antibiotics, and systemic doxycycline were allowed. Standard antiemetics included prednisolone, ondansetron, and metoclopramide.

If consent was withdrawn or if the experimental treatment was postponed for >4 weeks, i.e. >6 weeks between two treatments, the patient was excluded from the study.

The trial was conducted according to good clinical practice guidelines [17] and monitored by an independent monitoring unit. Inclusion criteria and response evaluations were monitored in every patient while other data were monitored in every three patients.

study evaluations

All patients with biliary tract cancer were potential candidates for the protocol and were screened with medical history, physical examination, recording of performance status, computed tomography scan of chest and abdomen, blood chemistries, blood counts, and *KRAS* evaluation. A screening log was recorded.

During treatment, blood counts were repeated before every treatment, blood chemistries and evaluation of toxicity were repeated at every 4 weeks, and physical examination, evaluation of performance status, and tumor evaluation were repeated every third cycle. If treatment was stopped before progression, the patient was followed clinically and radiologically every 3 months until progression. After progression, only date and cause of death were recorded. Treatment after exclusion from the study was according to the department's guidelines.

statistics

The primary end point was the fraction of patients alive without progression at 6 months (180 days) and secondary end points were median progression-free survival (PFS), response rate (RR), toxicity, and median overall survival (OS).

The trial was based on a modification of Simon's two-stage design with 6–months PFS instead of response. The target for PFS at 6 months was 60% and the treatment was considered uninteresting if below 40%. The risk of type 1 and 2 error was set at 0.05 and 0.2, respectively. With these constraints, 7 out of the first 16 patients should be progression free at 6 months in order to include a total of 46 patients. A priori, if at least 23 patients met the primary end point, the treatment is a candidate for further evaluation in a confirmatory study.

Nonparametric methods (including Wilcoxon and Mann–Whitney test or Fisher's exact test) were used to compare patient characteristics, toxicity, and RRs.

Time-to-event end points (PFS and OS) were estimated by the Kaplan–Meier method and were calculated from date of study entry. Response was calculated for patients with measurable disease at baseline. The best response was recorded and clinical progression or death before the first evaluation was considered progressive disease. The RR was defined as the fraction of patients with partial response (PR) or complete response (CR) according to the RECIST version 1.0 [18]. Responses were not required to be confirmed after 4 weeks as RR was not the primary end point.

Categorical variables were compared using Fisher's exact test, and 95% two-sided confidence intervals (CI) were constructed for all parameter estimates.

All patients were analyzed for PFS and OS. Patients receiving at least one cycle were analyzed for RR and PFS at 6 months unless consent was withdrawn or treatment was postponed for >4 weeks before the first evaluation at 3 or 6 months, respectively. All who received at least one dose of study medication were evaluated for safety. Toxicity was evaluated using Common Terminology Criteria for Adverse Events version 3.0 (National Cancer Institute).

results

baseline

From October 2008 to August 2010, 112 patients were screened for eligibility in a single institution and 46 were included. Figure 1 shows the reasons for patients to be ineligible and the number of patients included in the analysis. Most patients were excluded because of major deviations of the eligibility criteria (*KRAS* not wild type, performance status > 2, not biliary tract cancer, psychiatric disorder, significant comorbidity, biochemistry, other concomitant malignancy, or previous treatment). Only six patients preferred the departmental standard treatment to trial treatment. Of the included patients, there were 31 women and 15 men. Median age was 66 years (range 37–80). Patients who were in a performance status of 0, 1, and 2, were 25, 16, and 5, respectively, in number. Baseline characteristics are shown in Table 1.

treatment

The median number of finished treatment cycles was 5 (range 0–12 cycles). Time from study entry to start of last cycle ranged from 0 to 324 days, with a median of 146 days. The reasons for stopping treatment were progression ($n = 15$), patient wish for a treatment break ($n = 10$), toxicity ($n = 9$), treatment delay ($n = 4$), death ($n = 6$), and other reasons ($n = 2$). Dose reduction of at least 20% of any of the drugs, but especially oxaliplatin, was indicated in most patients (37 of 46 patients), while unplanned postponement for >10 days only was seen in 7 of 46 patients.

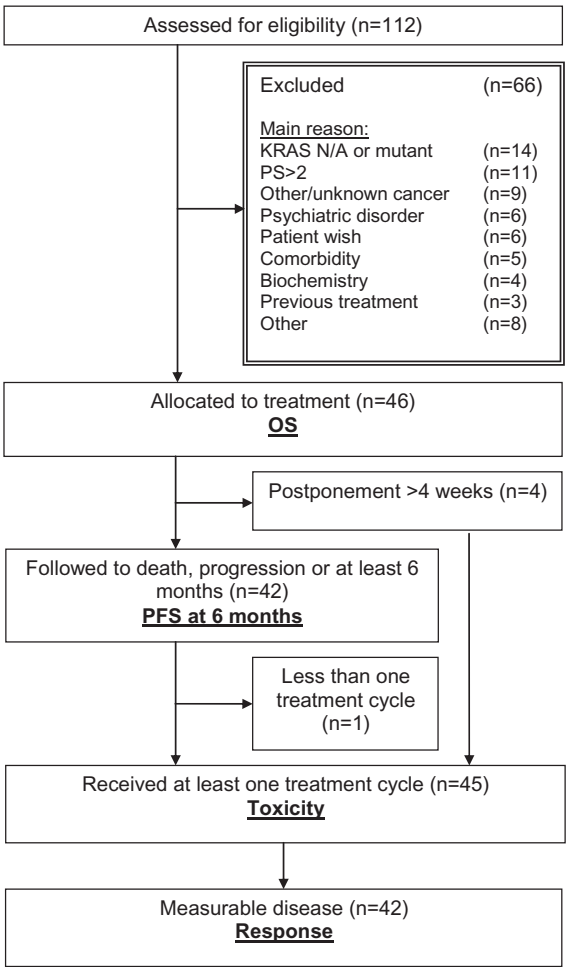

Figure 1. Study flow diagram showing all patients screened for inclusion in the study and reasons for ineligibility. Furthermore, it is shown which patients were included in efficacy analysis (PFS at 6 months, OS, and response evaluation) and toxicity analysis (bold and underlined). N/A, not available; OS, overall survival; PFS, progression-free survival; PS, performance status.

efficacy

Four patients alive and without progression were excluded from the study before 6 months because of postponement of treatment for >4 weeks as determined in the protocol. In one patient, the postponement was indicated in order to gain acceptable performance status and in three patients, postponement was caused by biliary obstruction, infection and in one case also pancreatitis. This left forty-two patients eligible for the primary end point. Eleven patients progressed or died before 6 months and thus the fraction of a 6-month PFS was 74% (95% CI 58% to 84%).

Forty-two patients had measurable disease, received at least one treatment cycle, and were therefore eligible for response evaluation. The best response was 1 CR, 13 PR, and 22 stable disease (SD). Six patients progressed or died at or before first assessment after 3 months. Accordingly, RR was 33% (95% CI 21% to 49%) and the disease control rate 86% (95% CI 72% to 94%).

Figure 2 shows the Kaplan–Meier plot of PFS. Median PFS was 8.3 months (95% CI 6.8–8.7 months). At the time of data analysis, 33 patients had died. The median OS was 10.0 months (95% CI 7.4–12.7 months, intention to treat, Figure 2). Efficacy estimates are summarized in Table 2.

Table 1. Patient characteristics at baseline

Variable	
Age	
Median (range), years	66 (37–80)
Sex, *n*	
Female	31
Male	15
Performance status, *n*	
0	25
1	16
2	5
Time from primary diagnosis to inclusion	
Median (range), days	35 (7–1191)
Localization, *n*	
Intrahepatic	10
Perihilar	7
Extrahepatic	21
Unclassified	8
Stage, *n*	
Locally advanced	7
Metastatic	39
Metastases, *n*	
Lymph nodes	30
Liver	30
Peritoneum	13
Lung	8
Bone	1
Surgery, *n*	
Yes	8
No	38

toxicity

Forty-five patients received at least one treatment cycle and were eligible for toxicity assessment. Table 3 depicts drug-related toxic effects both in absolute numbers for grade 1 to 4 and in relative numbers for grade 3 or grade 4 toxicity. Infections are very frequent in biliary tract cancer patients but only in 9% of the patients, grade 3 infection was suspected to be directly related to therapy. There was only one case of febrile neutropenia. Oxaliplatin was reduced if neurotoxicity developed, but only 7% developed grade 3 sensory neurotoxicity and there was one case of grade 3 motor toxicity. An EGFR-related skin rash grade 3 or higher was seen in 20% of the patients. Treatment of the rash was initiated after clinical evaluation and was not given prophylactic.

discussion

The purpose of the present trial was to evaluate the efficacy of chemotherapy and panitumumab in patients with biliary tract cancer. We designed a marker-driven phase II trial directing only *KRAS* wild-type tumors to the treatment. This approach has never been used before and therefore we chose a two-stage design with stopping rules and included the minimum of patients that would allow a reasonable efficacy estimate.

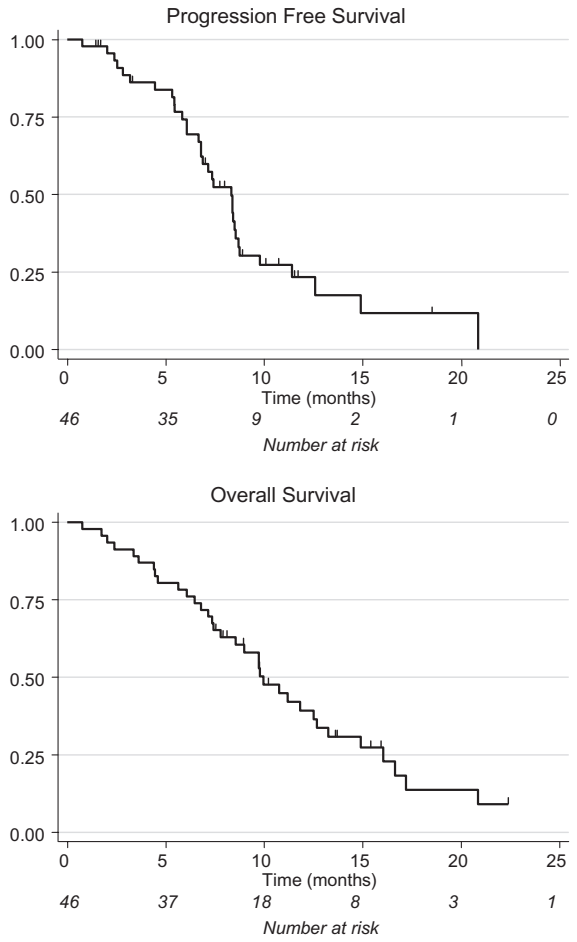

Figure 2. Kaplan–Meier curves for progression-free and overall survival.

Table 2. Efficacy estimates of fraction of progression-free survival (PFS) at 6 months, response and, according to Kaplan–Meier, median PFS and overall survival (OS)

	Denominators	Number (%; 95% CI)
PFS at 6 months	42	11 (74; 58–84)
Response	42	
Complete response	1	1 (2; 0.1–13)
Partial response	13	13 (31; 19–46)
Stable disease	22	22 (52; 38–67)
Progressive disease	6	6 (14; 6–28)
Overall response rate	14	14 (33; 21–49)
Disease control rate	36	36 (86; 72–94)
Median PFS	46	8.3 months (; 6.8–8.7)
Median OS	46	10.0 months (; 7.4–12.7)

CI, confidence interval.

Data about the rate of *KRAS* wild type in an unselected cohort of biliary tract cancer patients eligible for chemotherapy is sparse and the rate may differ from that in cohorts of newly diagnosed or operated patients. At the time of planning the trial, ~55% was expected to be wild type [19]. Later reports in European patients suggest 90% wild type [20] and 62% in Chinese patients [21]. In our study, 98 (87.5%) of 112 screened tumors were wild type and the rest were mutated or had no adequate DNA available.

Table 3. Number and grade of most frequent drug-related toxic effects

Grade	1 *n*	2 *n*	3 *n*	4 *n*	3 or 4 %
Nausea	20	6	2	0	4
Infection	14	4	4	0	9
Vomiting	14	3	1	0	2
Febrile neutropenia	1	0	1	0	2
Stomatitis	18	5	2	0	4
Neuropathy, sensory	20	7	3	0	7
Diarrhea	16	3	2	0	4
Neuropathy, motor	4	4	1	0	2
Obstipation	16	5	0	0	0
EGFR-related rash	16	13	8	1	20
Pain	22	6	2	0	4
Hand and foot reaction	14	7	2	0	4

The last column shows the relative frequency in % of grade 3 or grade 4 toxicity.
EGFR, epidermal growth factor receptor.

It is not known if *KRAS* mutations in biliary tract cancer are negative predictors for the effect of anti-EGFR treatment. Based on data from colorectal cancer indicating a lack of effect in *KRAS*-mutated tumors [16], we chose not to include these patients. Later data have even pointed toward a detrimental effect of EGFR inhibition in *KRAS*-mutant cases [22]. In a trial with gemcitabine, oxaliplatin, and cetuximab, three patients had *KRAS*-mutant tumors and their best response was one SD and two PR [20], rendering the question of treating these patients still open. A cautious approach would be to restrict anti-EGFR antibodies to *KRAS* wild type until proven beneficial there and then afterward test it in *KRAS*-mutant cases. In an ongoing parallel phase II trial, we are including patients with *KRAS*-mutant tumors and are treating them with combination chemotherapy [23]. Another area of future research is the effect of other self-activating mutations in the EGFR pathway such as *BRAF* mutations.

Some of the disadvantages of single-arm phase II studies are the high risk of selection bias and the low external validity and therefore comparisons of efficacy data between studies should be done with caution. We found that the primary end point was 74.2% PFS at 6 months. Secondary end points were an RR of 33% and median PFS and OS of 8.3 and 10.0 months, respectively. There are no other comparable data on the effect of panitumumab in biliary tract cancer, but in a few studies, cetuximab has been evaluated [24]. In the trial by Gruenberger et al. [20], 30 patients received gemcitabine, oxaliplatin, and cetuximab. They found a remarkably high RR of 63% and median PFS and OS were 8.8 and 15.2 months, respectively. Preliminary results from a randomized phase II trial with gemcitabine and oxaliplatin with or without cetuximab showed a more modest 11% RR in the first 18 patients treated with the triplet. PFS was 7 months in the cetuximab arm and 5 months in the chemotherapy-only arm (101 patients) [25].

Only randomized trials can tell if there is any clinical benefit from adding an EGFR inhibitor to combination chemotherapy. In a phase III trial, the combination of gemcitabine and cisplatin has resulted in an RR of 26%, PFS of 8.0 months, and

OS of 11.7 months [4]. The chemotherapy triplet used in the present study has, without panitumumab, shown an RR of 34%, PFS of 6.9 months, and OS of 12.5 months in a phase II trial [5]. The apparent minor differences in efficacy call for future large randomized phase III trials to decide both the superior chemotherapy combination and the effect of adding an EGFR antibody. Unfortunately, another approach to inhibit EGFR by adding the small-molecule protein kinase inhibitor erlotinib to gemcitabine and oxaliplatin did not show superiority compared with chemotherapy alone [26]. Whether erlotinib has effect in subgroups of biliary tract cancer or whether other targeted agents are more efficacious has yet to be determined [27].

This is the first marker-driven phase II trial in irresectable biliary tract cancer. Three in four patients were alive without progression at 6 months and the median OS was 10.0 months. Toxicity related to chemotherapy was acceptable and the most frequent side-effect to panitumumab was skin rash. The marker-driven approach and the treatment combining chemotherapy with panitumumab in patients with *KRAS* wild-type tumors was feasible and met the efficacy criteria for future testing in a randomized trial.

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disclosure

The authors declare no conflicts of interest.

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