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A Phase II Trial of Fixed-Dose Rate Gemcitabine plus Capecitabine in Metastatic/Advanced Biliary Tract Cancer Patients

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Key Words
Capecitabine · Fixed-dose rate · Gemcitabine · Biliary tract cancer

Abstract
Background: This phase II trial was conducted to determine the activity and safety of the combination of fixed-dose rate (FDR) gemcitabine and capecitabine in metastatic biliary tract cancer (BTC) patients. ***Methods:*** Patients with unresectable BTC who had pathologically confirmed adenocarcinoma, no prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status ≤1 and measurable disease were enrolled. Treatment consisted of FDR gemcitabine at 800 mg/m^2 on days 1 and 8 every 21 days with capecitabine administered orally b.i.d. in equal doses (650 mg/m^2 b.i.d.) for 14 days (28 doses). ***Results:*** Between May 2005 and February 2009, 30 patients were enrolled. The median age was 67 years (45–76) and there were 14 males. Thirty patients were evaluable for response and toxicity. A total of 221 cycles were administered (median 7, range 2–16). One patient achieved complete response and 7 patients achieved partial response, giving an overall response rate of 26.7% in the intention-to-treat population. Twelve patients (40.0%) had stable disease. The median progression-free survival was 6.33 months. The median overall survival was 10.8 months. Grade 3/4 neutropenia and thrombocytopenia were noted in 13 and 7% of the patients, respectively. Grade 2/3 nonhematologic toxicities were asthenia (54% of patients), diarrhea (17%), stomatitis (23%) and hand-foot syndrome (7%). There was no treatment-related death. The drugs taken were skipped at least once in 45% of the patients and the dose was reduced in 26% of them. ***Conclusions:*** The combination of FDR gemcitabine and capecitabine in this 3-week cycle is safe and seems to have a good activity in advanced biliary cancer.

Introduction

Biliary tract cancers (BTC) are relatively rare tumors with a dismal prognosis [1]. This kind of tumor is more likely to occur in patients aged between 50 and 70 years. As far as the role of nonsurgical oncologic treatment is concerned, the only standard regimen for advanced disease has recently been established. In fact, the ABC-02 study, a practice-changing phase III study, recognized the

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gemcitabine/cisplatin regimen as the standard of care, with a stable disease rate of 81%, progression-free survival (PFS) of 8 months and median overall survival (OS) of 11.7 months. Due to clinical conditions, patients who receive palliative chemotherapy are usually treated with single-agent gemcitabine or with combination regimens including mitomycin or fluoropyrimidines [2, 3]. Response rates with these treatments range from 10 to 35%, and median OS time varies between 5 and 12 months [4]. Nevertheless, the small number of published trials and the considerable variability in the patients' clinical characteristics make the data difficult to interpret. Nowadays, there is no standard chemotherapy regimen in BTC. Several reports have demonstrated that gemcitabine is active in BTC [5–7]. Capecitabine (Xeloda™; Hoffmann-La Roche, Basel, Switzerland) is an oral fluoropyrimidine carbamate that selectively generates 5-FU in tumor tissues. Gemcitabine also appears to modulate the activity of 5-fluorouracil (5-FU) in renal and gastrointestinal malignancies [8, 9]. Capecitabine offers the possibility of continuous tumor exposure to 5-FU by preferential activation at the tumor, while potentially minimizing the exposure of healthy body tissues to systemic 5-FU [10, 11]. Moreover, 5-FU has demonstrated activity in BTC [12]. As shown in our phase I study, to enhance the cytotoxic activity of gemcitabine, an alternative infusion regimen has been explored [13]. As the active metabolite of gemcitabine, 2′,2′-difluorodeoxycytidine triphosphate (dFdCTP), has a long intracellular half-life, a fixed-dose rate (FDR) infusion of 10 mg/m^2/min has been shown to lead to maximal intracellular accumulation. In particular, it has been demonstrated that increasing the infusion time while holding the dose rate constant at 10 mg/m^2/min could result in increased intracellular levels of dFdCTP, thus enhancing the activity of gemcitabine [14, 15]. On the basis of phase I results, the dose of FDR gemcitabine 800 mg/m^2 in 80 min on days 1 and 8 plus capecitabine 650 mg/m^2 b.i.d., for 14 consecutive days followed by 1 week of rest, is a recommended schedule that we used in this study. This is a phase II study evaluating toxicity, response, and survival associated with using a combination of FDR gemcitabine and capecitabine to treat patients with unresectable or metastatic BTCs.

Patients and Methods

Eligibility

Patients with histologically confirmed unresectable or metastatic BTC adenocarcinomas, including those who were at least 18 years old and who had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1, were considered suitable for the study. The following hematologic and chemistry parameters were recommended: absolute neutrophil count 1,500/mm^3, platelet count 100,000/mm^3, hemoglobin 10.0 g/100 ml, preserved renal function (serum creatinine 1.6 mg/dl, normal creatinine clearance), and hepatic function (total bilirubin 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase 2.5× normal without hepatic metastasis and 4× normal with hepatic metastasis, serum alkaline phosphatase <2.5× the upper limit of normal or <5× the upper limit of normal if liver metastases were present or <10× the upper limit of normal if bone metastases were present). A basal cardiac function evaluation was required.

Major exclusion criteria included radiotherapy or chemoradiotherapy treatment within the previous 4 weeks (6 weeks if the previous therapy included nitrosourea or mitomycin C). Patients previously treated with chemotherapy for metastatic disease were excluded. Concomitant use of amiodarone, ketoconazole, itraconazole, diltiazem, verapamil, barbiturates, and warfarin was not permitted. Pregnant or lactating patients were excluded from the study. Patients with significant stomach, small intestine, liver, or kidney disease likely to affect drug absorption or metabolism were excluded from the study. Other contraindications included a history of coagulopathy or brain or other central nervous system metastases. Patients with any history of a previous malignancy diagnosed within 5 years were also excluded, with the exception of basal cell carcinoma or skin and cervical carcinoma in situ. Additionally, patients were excluded if adequate follow-up was not possible (geographic difficulties, no compliance with necessary clinical-instrumental investigations, etc.).

All patients were required to provide written informed consent before initiation of treatment after a complete and clear explanation. Approval of the local ethics committee was obtained. The trial was conducted in accordance with the declaration of Helsinki.

Treatment and Dose Modifications

Capecitabine (650 mg/m^2 b.i.d.) was administered orally twice a day for 14 consecutive days followed by 1 week of rest. It was supplied as film-coated Xeloda tablets in two dosage strengths, 150-mg and 500-mg tablets, administered in nonfasting conditions and swallowed with water. Gemcitabine (Gemzar™) was given at an FDR dose of 800 mg/m^2 in 80 min on days 1 and 8 of each cycle. The drug was prepared for administration according to the directions in the package. Cycles were repeated every 21 days. All patients had their medical history taken and had a full physical examination with radiologic and laboratory evaluations. History, physical examination, and laboratory tests were repeated on day 1 of each cycle of therapy. Prophylactic administration of recombinant human granulocyte colony-stimulating factor was not allowed. In cases where the patient had grade 3 or 4 afebrile neutropenia, subsequent cycles were repeated with recombinant human granulocyte colony-stimulating factor, and capecitabine and gemcitabine doses were reduced by 25%. In cases of grade 3 or 4 thrombocytopenia lasting more than 7 days, the doses of both drugs were also reduced by 25%. The doses of capecitabine were reduced by 25% in cases of grade 3 or 4 diarrhea or hand-foot syndrome.

Efficacy and Safety Evaluation

Tumor assessment according to RECIST criteria was performed at 9-week intervals by the investigators [16]. Tumor lesions

were assessed by computed tomography scanning, X-rays or magnetic resonance imaging. Responding patients or those with stable disease (SD; >3 months) could continue treatment until progression of disease (PD), unacceptable toxicity or their decision to stop. PFS was calculated as the time from the time of inclusion in the study to the first record of PD or the date of death if the patient died before PD was demonstrated. Survival was monitored every 3 months after the patient completed treatment. Safety was monitored during the study and for 28 days after the last cycle treatment. Adverse events were graded according to the National Cancer Institute of Canada-Common Toxicity Criteria (NCI-CTC) [17]. PFS and OS were analyzed by the Kaplan-Meier method. Those patients who did not receive at least one dose of study medication or for whom no follow-up safety information was available were excluded.

Statistical Analysis

The Simon optimal two-stage design was chosen for sample size calculation. The expected number of patients for accrual in this study was calculated to reject a 10% response rate in favor of a target response rate of 30%. This condition allows a significance level of 0.05 with a statistical power of 90%. The preliminary activity of this new combination will be assessed enrolling 9 patients. If there was <1 response, accrual needed to be terminated. Otherwise, 21 additional patients need to be entered in the second stage to achieve a target sample size of 30 evaluable patients for tumor response. If more than 4 responses were observed in these 30 patients, further assessment could be suggested. RECIST criteria were considered for the evaluation of response. Kaplan-Meier survival curves were generated based on the PFS and OS data and analyzed by the log-rank statistic.

Results

Patient Characteristics

Thirty patients were enrolled between May 2005 and February 2009. The median age was 67.0 years (range 45–76); there were 17 (55%) females and 14 (45%) males. All patients completed the first two cycles of therapy and were, therefore, assessable for toxicity and for efficacy. ECOG performance status was 0 in 24 (77%) of patients and 1 in the other 7 (23%). Seven (23%) patients needed biliary drainage. The distribution of primary cancer was: gallbladder in 13 (42%) patients, ampulla of Vater in 2 (6%) patients, intrahepatic cholangiocarcinoma in 9 (29%) patients and extrahepatic bile duct in 7 (23%) patients. A total of 221 cycles were administered; the median number of cycles for a patient was 7.0 (range 2–16). The median follow-up was 22.3 months. As shown in table 1, the majority of patients (97%) had stage IV disease and the most commonly affected metastatic sites were liver (81%) and abdominal lymph nodes (35%).

Table 1. Patient characteristics

Characteristic	Number of patients
Evaluable patients	30 (97%)
Gender	
Male	14 (45%)
Female	17 (55%)
Age, years	
Median (range)	67 (45–76)
ECOG performance status	
0	24 (77%)
1	7 (23%)
Disease at presentation	
Locally advanced	1 (3%)
Metastatic disease	30 (97%)
Primary disease	
Gallbladder	13 (42%)
Ampulla of Vater	2 (6%)
Intrahepatic cholangiocarcinoma	9 (29%)
Extrahepatic bile duct cancer	7 (23%)
Metastatic sites	
Median (range)	1 (0–5)
Sites of metastatic disease	
Liver	25 (81%)
Lymph nodes	11 (35%)
Peritoneum	2 (6%)
Lung	1 (3%)
Others	4 (13%)

Table 2. Treatment-related toxicity

Toxicity	Number of patients (n = 30)			
	grade 1	grade 2	grade 3	grade 4
Hematologic				
Neutropenia	1 (3%)	9 (30%)	3 (10%)	1 (3%)
Leukopenia	3 (10%)	3 (10%)	2 (7%)	
Thrombocytopenia	3 (10%)	4 (13%)	2 (7%)	
Anemia	14 (47%)	5 (16%)		
Nonhematologic				
Nausea	13 (43%)	6 (20%)		
Diarrhea	9 (30%)	3 (10%)	2 (7%)	
Stomatitis	6 (20%)	6 (20%)	1 (3%)	
Elevated AST	4 (13%)			
Fatigue	8 (27%)	11 (37%)	5 (17%)	
HFS	3 (10%)	2 (7%)		

Toxicity was graded according to the second version of the Common Toxicity Criteria of the National Cancer Institute. AST = Aspartate aminotransferase; HFS = hand-foot syndrome.

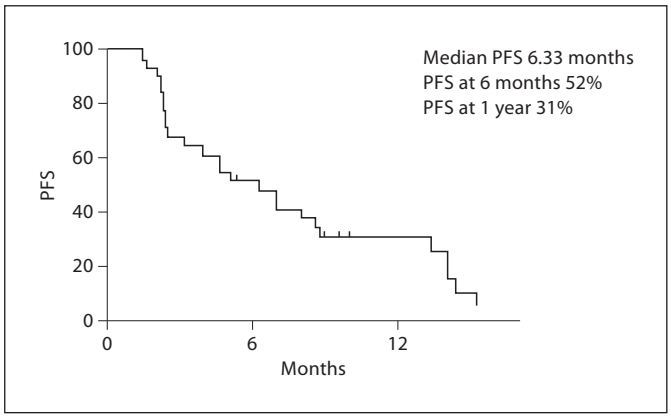

Fig. 1. PFS: median, at 6 months, and at 1 year.

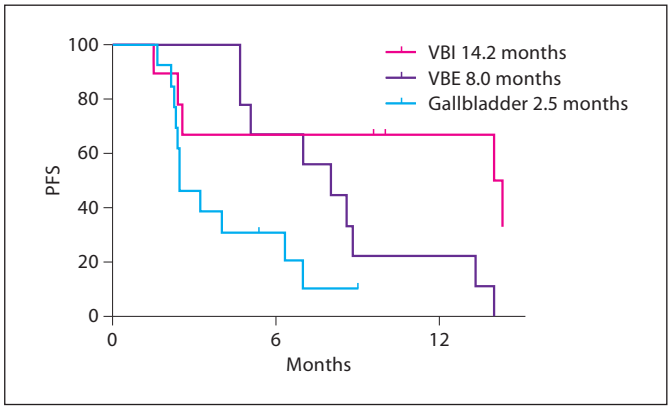

Fig. 2. PFS for primary sites: VBI, VBE and gallbladder.

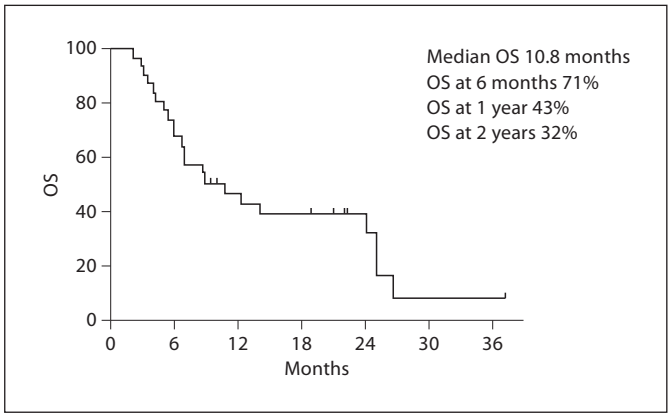

Fig. 3. OS: median, at 6 months, and at 1 and 2 years.

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Table 3. Therapeutic results

Result	Number of patients
Complete response	1 (3%)
Partial response	7 (23%)
SD	12 (40%)
PD	10 (33%)

Safety

Table 2 summarizes the observations on toxicity. Nonhematologic adverse events (G2 percentage/G3 percentage) were: nausea (20/0), hand-foot syndrome (7/0), general weakness (37/17), stomatitis (20/3), and diarrhea (10/7). One patient (3%) experienced G4 nonfebrile neutropenia. Grade 3 neutropenia, anemia, and thrombocytopenia were present in 10, 0 and 7% of patients, respectively. Eight patients (27%) had reduced drug doses for neutropenia (2), thrombocytopenia (1), diarrhea (2), general weakness (2), and hand-foot syndrome (1). Fourteen patients (47%) needed to delay chemotherapy because of neutropenia (5). No deaths occurred during the study which could be attributed to toxicity.

Efficacy

The median duration of treatment for all patients was 143 days (range 34–390 days). Seven (23%) of 30 evaluated patients (1 patient excluded for causes not associated with the tumor) obtained a partial response, 1 patient (3%) had a complete response, and 12 patients (40%) had SD obtaining tumor control (complete response + partial response + SD) of 66%. Ten patients (33%) had PD. The median PFS was 6.33 months. PFS were 52 and 31% at 6 months and 1 year, respectively (fig. 1). The subgroup analysis showed a PFS of 14.2, 8 and 2.5 months in intrahepatic biliary tract (VBI), extrahepatic biliary tract (VBE) and in gallbladder, respectively (fig. 2). The median OS for the entire population was 10.8 months (fig. 3). At 6 months, 1 year and 2 years, 71, 43 and 32% of patients were alive, respectively. Efficacy data are shown in table 3.

Discussion

At the moment, there is no standard chemotherapy regimen for advanced biliary cancer. Historically, chemotherapy had little impact on the natural history of this disease. There are several reasons for this: a lack of active agents, the overall morbidity of treatment and conse-

Table 4. Recent clinical trials of biliary cancer

Author, year, Ref. No.	Regimen	No.	Tumor sites	RR, %	OS, months
Gallardo, 2001 [20]	gemcitabine	26	gallbladder	35	7.5
Kuhn, 2002 [21]	gemcitabine/docetaxel	43	gallbladder + bile duct	9	11
Taieb, 2002 [22]	cisplatin/5-FU	29	gallbladder + bile duct	34	9.5
Nehls, 2003 [23]	capecitabine/oxaliplatin	29	gallbladder + bile duct	23	9.5
Reyes-Vidal, 2003 [24]	gemcitabine/cisplatin	44	gallbladder	45	7
Patt, 2004 [25]	capecitabine	26	gallbladder + bile duct	17	7
Eng, 2004 [26]	fixed-dose gemcitabine	15	bile duct	0	5
Kornek, 2004 [27]	mitomycin/gemcitabine vs. mitomycin/capecitabine	51	bile duct	20 31	6.7 9 (P no sign)
Knox, 2005 [28]	gemcitabine/capecitabine	45	gallbladder + bile duct	30	14
Rao, 2005 [29]	5-FU/leucovorin vs. ECF	54	bile duct	19 15	12 9 (P no sign)
Ducreux, 2005 [30]	5-FU vs. 5-FU/cisplatin	58	bile duct	7 19	5 8 (P no sign)
Julka, 2006 [31]	gemcitabine/oxaliplatin	20	gallbladder	36.7	ND
Lee, 2006 [32]	gemcitabine/oxaliplatin	24	bile duct	21	9.3
Philip, 2006 [33]	erlotinib	42	bile duct	7	ND
Manzione, 2007 [34]	gemcitabine/oxaliplatin	34	gallbladder + bile duct	41	10
Hong, 2007 [35]	capecitabine/cisplatin	32	gallbladder + bile duct	40.6	12.4
Riechelmann, 2007 [36]	gemcitabine/capecitabine	75	gallbladder + bile duct	29	12.7
Andre, 2008 [37]	gemcitabine/oxaliplatin	45	gallbladder + bile duct	33	8.3
Im, 2008 [38]	S1/cisplatin	51	gallbladder + bile duct	30	8.7
Furuse, 2008 [39]	S1	40	gallbladder + bile duct	35	9.4
Meyerhardt, 2008 [40]	gemcitabine/cisplatin	30	gallbladder + bile duct	21	9.7
Valle, 2009 [41]	gemcitabine vs. gemcitabine/cisplatin	86	gallbladder + bile duct	15 24	ND
Wagner, 2009 [42]	gemcitabine/oxaliplatin/5-FU	37 35	bile duct gallbladder	19 23	10 9.9
Sasaki, 2009 [43]	S1/gemcitabine	35	gallbladder + bile duct	34.3	11.6
Kim, 2009 [44]	gemcitabine/oxaliplatin	40	gallbladder + bile duct	15	8.5
Ramanathan, 2009 [45]	lapatinib	17	bile duct	0	5.2
Yamashita, 2010 [46]	gemcitabine/cisplatin/5-FU	21	bile duct	33.3	18.8
Sharma, 2010 [47]	gemcitabine/oxaliplatin	50	gallbladder	21.2	7.5
Jang, 2010 [48]	gemcitabine/oxaliplatin	53	gallbladder + bile duct	18.9	8.3

No. = Number of enrolled patients; RR = response rate; 5-FU = 5-fluorouracil; ECF = epirubicin, cisplatin, 5-fluorouracil; P no sign = not statistically significant; ND = not done.

quently reduced dose intensity, and the grouping together of different cancer types with different biologies. Older chemotherapy combinations with 5-fluorouracil have demonstrated response rates of less than 15%. To our knowledge, only one published randomized study has shown an improvement in quality of life for biliary cancer patients treated with 5-fluorouracil-based chemotherapy versus best supportive care, although no difference in OS was observed [18]. In table 4, the principal phase II studies are summarized, where regimens containing new agents such as gemcitabine, capecitabine, and oxaliplatin have demonstrated objective responses in 20–45% of patients and a median survival of 8–14 months. The recent approval of numerous targeted agents in a variety of solid tumors and hematologic malignancies has clearly demonstrated the clinical efficacy of such agents. How-

ever, the overall modest activity of these agents in 'orphan' tumors such as BTC emphasizes the need for novel and more effective medical treatment options such as combinations of targeted agents with cytotoxic drugs or with other novel anticancer drugs. In our study, the combination of FDR gemcitabine and capecitabine demonstrated an interesting activity and a favorable safety in patients with advanced and/or metastatic BTC. Despite the usual limitation of cross-study comparisons, these findings compare favorably with results previously reported for 5-FU/gemcitabine combinations in patients with advanced BTC. In addition to antitumor activity, safety is a critically important target for the choice of new treatment combinations. Our combination regimen has the advantage of convenience and practicability over continuous intravenous 5-FU plus either gemcitabine or cisplatin, and has a clear potential to reduce healthcare resource expenditure. This is because capecitabine is administered orally and avoids the complications related to the use of an implanted catheter required for the continuous intravenous administration of 5-FU. In our experience, the toxicity profile is acceptable especially when compared with the toxicities reported in comparable studies. Grade 3 neutropenia and asthenia were reported in 10 and 16%, respectively, and these data are superimposed with the data reported in the literature. Biliary tumors can occur anywhere in the hepatobiliary system and are often classified according to location. In the present study, cholangiocarcinoma (VBI + VBE) appeared to respond better than gallbladder carcinoma (PFS: 8.7 vs. 2.5 months, $p = 0.005$), obtaining a major OS (25 vs. 6 months, $p = 0.001$), even if the interpretation of data is difficult because of the relatively small number of patients and the different biological and prognostic behavior of the single isotypes.

Conclusions

Further research in this area should be directed at finding the best cytotoxic agent for a combination with capecitabine or gemcitabine or altering the dose intensity or route of administration in advanced BTC. Conventional chemotherapeutic drugs have achieved only modest results in patients with BTC. Therefore, innovative therapeutic approaches are needed to obtain significant results in this type of patients. The first standard of care has been proposed at ASCO 2009 [19]. In fact, the combination of cisplatin and gemcitabine has been shown to be more effective than gemcitabine alone in a multicenter randomized phase III trial [2], and new phase III trials evaluating a different combination of chemotherapy are needed. Due to the small number of patients and the inclusion of all biliary types (ampullary, gallbladder, bile duct) in this study, these results cannot be translated in clinical practice. A larger randomized phase III trial of our combination regimen compared with gemcitabine plus cisplatin needs to be conducted to validate the efficacy of FDR gemcitabine plus capecitabine in metastatic/advanced BTC patients. Several trials are ongoing with the aim to explore the activity of the combination of chemotherapeutics with different targeted drugs inhibiting different pathways. The results of the ongoing trials are keenly awaited to definitely identify the most effective strategy in BTC.

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