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ORIGINAL ARTICLE

Phase II study of capecitabine and cisplatin in previously untreated advanced biliary tract cancer

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Abstract
Background Biliary tract cancer is one of the most aggressive and chemotherapy-refractory tumors. Although only curative treatment modality is surgery, most patients are not suitable for surgery due to advanced stage of the disease at diagnosis. Thus most patients with biliary tract cancer are possible candidates for palliative chemotherapy. The standard chemotherapeutic regimen is still to be defined, however. We performed a phase II study of combination chemotherapy with capecitabine and cisplatin in these patients to evaluate efficacy and toxicity of the regimen.
Methods Patients with previously untreated metastatic, recurrent, or inoperable biliary tract cancer were enrolled. Eligible patients were screened as following: (1) histologically confirmed, (2) age between 18 and 75 years, (3) at least one measurable lesion according to RECIST criteria, (4) ECOG performance status ≤ 2, (5) a life expectancy of at least 3 months, and (6) adequate laboratory values. Patients received capecitabine (2,500 mg/m^2/day, days 1 to 14) and cisplatin (60 mg/m^2, day 1) every 3 weeks. Response was assessed for every two cycles of chemotherapy and treatment was stopped when tumor had progressed or stable with no further response.
Results Thirty-two patients were enrolled, 20 (62.5%) were male and 12 (37.5%) were female and the median age was 54 years (33–71 years). Fifteen patients (46.9%) had gallbladder cancer, 13 (40.6%) had intrahepatic cholangiocarcinoma, and 4 (12.5%) had extrahepatic biliary cancer. The most frequent metastatic sites were lymph nodes (20/32, 62.5%) and liver (28/32, 56.3%). No complete response was observed and partial response was observed in 13/32 patients. By the intent-to-treat analysis, the overall response rate was 40.6% (95% CI, 23.7–59.4) with 0 CR and 13 PRs. Stable disease was observed in 3 patients (9.4%), and 11 patients (34.4%) had progressive disease. The median time to progression was 3.5 months (95% CI, 1.3–5.8), and the median overall survival was 12.4 months (95% CI, 6.3–18.5) after the median follow-up duration of 9.5 months (4.8–26.1 months). A total of 108 cycles of chemotherapy was delivered. Grade 3 hematologic toxicities included neutropenia (5, 15.6%), anemia (1, 3.1%), and thrombocytopenia (1, 3.1%) per patient, and no grade 4 hematologic toxicities were observed. Grade 3 non-hematologic toxicities included hyperbilirubinemia (2, 6.3%), increase of alkaline phosphatase (2, 6.3%), hand–foot syndrome (2, 6.3%), anorexia, and diarrhea (1, 3.1%) per patient, respectively. There was no treatment-related death.
Conclusion The combination chemotherapy of capecitabine and cisplatin demonstrated a promising antitumor activity with mild toxicity profile in patients with advanced biliary tract cancer.

Keywords Biliary tract cancer · Cholangiocarcinoma · Gall bladder cancer · Capecitabine · Cisplatin

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Introduction

Biliary tract cancers are uncommon cancers in the western countries accounting for approximately 4% of gastrointestinal malignancies [1, 2] and highly aggressive tumors with reported 2-year survival rates of 13–26% [2, 3]. In Korea, biliary tract cancers are more common and annually 3,500 new patients are diagnosed of biliary tract cancers accounting for 6% of all cancer deaths [4]. The only curative treatment for biliary tract cancers remains surgery. However, the surgical management is often complex and difficult with high morbidity and mortality rates due to its extensiveness in resection; only one-third of the patients initially present with resectable disease [5, 6]. Moreover, even patients who have undergone surgery eventually have a recurred disease after all [7]. Thus, most patients with biliary tract cancers are possible candidates for palliative systemic chemotherapy; however, the optimal chemotherapeutic regimen has not been defined yet.

As with most gastrointestinal tumors, 5-fluorouracil (5-FU) is the most studied drug as a single agent or a combination in different dosages and schedules with response rates of 0–30% and with median survival of 7–9 months in biliary tract cancers [8–12]. Ducreux et al. [13] reported combination chemotherapy of 5-FU and cisplatin in biliary tract cancers that showed moderate antitumor activity with 24% of overall response rate, but 5-FU administration needed hospitalization and central venous access frequently for continuous infusion. Capecitabine is a novel oral fluoropyrimidine carbamate, which is converted to 5-FU in tissues and showed comparable efficacy and toxicity with 5-FU in pre-linical studies [11]. Capecitabine is mimicking continuous infusion of 5-FU and more convenient in administration. Single-agent capecitabine showed a response rate of 19% in advanced hepatobiliary cancers in one study [14], and also produced promising antitumor activity with tolerable safety profiles in patients with other gastrointestinal cancers in a single-agent or a combination with other drugs [15, 16]. Recently, some authors preliminarily reported combination of capecitabine and cisplatin showed better results than combination of 5-FU and cisplatin in terms of overall response rate in patients with advanced gastric cancer [17]; thus capecitabine could be thought to take places of 5-FU. Moreover, capecitabine is more convenient than 5-FU in unnecessary hospitalization and central catheterization.

In an attempt to develop a more effective and convenient chemotherapeutic regimen, we performed a phase II study of combination chemotherapy with capecitabine and cisplatin in these patients.

Patients and methods

Patient eligibility

Patients with previously untreated metastatic, recurrent, or inoperable biliary tract cancers were enrolled. Eligible patients were screened as following: (1) histologically confirmed adenocarcinoma of biliary tracts, (2) age between 18 and 75 years, (3) at least one measurable lesion according to the RECIST (response evaluation criteria in solid tumors) criteria, (4) ECOG (Eastern Cooperative Oncology Group) performance status $\leq$2, (5) a life expectancy of at least 3 months, and (6) adequate hematologic parameters (hemoglobin $\geq$9.0 g/dl, absolute neutrophil count (ANC) $\geq$1,500 per μl, platelet count $\geq$100,000 per μl), renal functions (serum creatinine $\leq$1.5 mg/dl or calculated creatinine clearance by Cockroft formula $\geq$50 ml/min), and hepatic function (aspartate aminotransferase, alanine aminotransferase $\leq$3$\times$ upper limits of normal, total bilirubin $\leq$2$\times$ upper limits of normal). Patients with metastatic tumors of central nervous system, prior history of another malignancy within 5 years of study entry except for basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix, were excluded from this study. All patients provided written informed consent before they entered the study, which was approved by the institutional ethics committee guidelines.

Treatment and dose modification

Patients received capecitabine 2,500 mg/m^2/day from day 1 to day 14 and cisplatin 60 mg/m^2/day on day 1. Treatment cycles were repeated every 3 weeks until the evidence of disease progression, unacceptable toxicity, patient's refusal or lost to follow-up, or showed stable disease with no responses after maximal responses. Cisplatin administration was preceded by adequate hydration to protect renal functions and through peripheral venous access on an outpatient basis. Capecitabine was prescribed for 2 weeks on patients' visit for cisplatin administration. Compliance to capecitabine was monitored by counting their remaining pills on each outpatient visit. A 5-hydroxytryptamine type 3 receptor antagonist was given as emesis prophylaxis before cisplatin administration.

Application of capecitabine was delayed until ANC $\geq$1,500 per μl, platelet $\geq$75,000 per μl, and recovery from non-hematologic toxicity to baseline or grade $\leq$1. If ANC and platelet counts were recovered to $\geq$1,500 per μl, and $\geq$75,000 per μl, respectively, capecitabine was given as same dose in case of a 1 week delay and 25% reduced dose in case of a 2 week delay. If patients

required a delay of longer than 2 weeks for recovery, patients went off the study protocol. Capecitabine was reduced by 25% of previous dose in case of CTC grade 3 or greater hand–foot syndrome, abnormal liver functions, and mucositis. Once a dose reduction was required, reescalation of dose was not allowed.

Assessment of efficacy and toxicity

The primary endpoint of this study was response rate and secondary endpoints were toxicity, overall survival, and time to progression. Pre-reatment evaluation included taking a full medical history and physical examination, complete blood cell count with differential counts, chemistry profiles, chest X-ray, computed tomography (CT) scan of measurable disease sites with intravenous administration of non-onic contrast media, and any other diagnostic procedures as clinically indicated. During treatment, a history taking, physical examination, assessment of toxicity, complete blood cell count with differentials, and blood chemistry were performed every 3 weeks before each cycle. Appropriate imaging studies including CT scans of abdomen and pelvis were taken every two cycles (6 weeks) to assess treatment response, and sooner if needed for documentation of disease progression. Patients were assessed every 2 months for disease progression following the completion of the chemotherapy. Responses were classified according to RECIST criteria. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response was calculated from the first day of documented response to the date on which progression of disease was first observed or date of last follow-up. Time to progression was calculated from the first day of treatment to the date on which progression of disease was first observed or date of last follow-up. Overall survival was calculated from the first day of treatment to the date of death or date of last follow-up. Toxicities were monitored according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale version 3.0.

Statistical consideration

According to the Simon's two-stage phase II optimal design [18], a sample size of 29 was required to accept the hypothesis that the true response rate is greater than 30% with 80% power, and to reject the hypothesis that the response rate is less or equal than 10% with 5% significance. In the initial stage, 10 evaluable patients were to be entered into the study and evaluated for response. If there was less or equal than 1 response, accrual was to be terminated. If 2 or more responses were observed in the first stage, then 19 additional patients were to be entered in the second stage to achieve a target sample size of 29 evaluable patients. If there were 5 or less responders among 29 evaluable patients, this trial would have been negative otherwise positive. Assuming that 10% of patients were inassessable, at least a total of 32 patients were planned to be accrued for this study.

Descriptive statistics were reported as proportions and medians, chi square test was adopted for P value, and 95% confidence interval (95% CI) for response rate was estimated following binomial distribution [19]. Overall survival (OS) and time to progression (TTP) were assessed by the Kaplan–Meier method and the 95% confidence interval (95% CI) for the median time to event was computed by the Greenwood's formula [19]. All analyses were conducted using Stata version 9.2 and SPSS version 12.0 K. The dose intensity (DI) was calculated as the ratio of the total dose (expressed in milligrams) per square meter of the patient, divided by the total treatment duration expressed in days. The relative DI was calculated as the ratio of the DI actually delivered to the DI planned in the protocol.

Results

Patient characteristics

Between September 2003 and February 2006, 32 patients were enrolled and their clinical characteristics are shown in Table 1. The median age of the patients was 54 years (range, 33–71), 20 patients (62.5%) were male and 12 patients (37.5%) were female. Most patients had good performance status, and all patients had metastatic or recurrent disease at study entry. There were 13 cases of intrahepatic cholangiocarcinoma (40.6%), 15 cases of gall bladder cancer (46.9%), and 4 cases of extrahepatic bile duct cancer (12.5%). Of 27 patients with initial metastatic disease, 4 patients had undergone palliative surgery. Of 5 patients with recurrent disease, 1 patient received adjuvant radiation therapy. No patient was exposed to chemotherapeutic agents previously. The most frequent metastatic sites were lymph nodes (20/32, 62.5%) and liver (18/32, 56.3%). Initial serum CA19-9 level was 593.89 IU/ml in median value (range 8.74–28,494 IU/ml).

Drug delivery

Drug delivery and relative dose intensity are shown in Table 2. In total, 108 cycles of chemotherapy were administered with a median of two cycles per patient

Table 1 Patient characteristics

	No. of patients	Percent
Characteristics	32	100
Primary site		
Intrahepatic bile duct	13	40.6
Gall bladder	15	46.9
Extrahepatic bile duct	4	12.5
Age, years (range)	Median 54 (33–71)	
Sex		
Male	20	62.5
Female	12	37.5
ECOG PS		
0–1	29	90.6
2	3	9.4
Presentation of initial disease		
Initial metastatic disease	27	84.4
Palliative surgery	4	12.5
No surgery	23	71.8
Relapsed after resection	5	15.6
Previous adjuvant chemotherapy	0	0
Previous adjuvant radiation	1	3.1
Site of metastasis		
Liver	18	56.3
Lymph nodes	20	62.5
Lung	9	28.1
Peritoneal seeding	6	18.8
Bone	2	6.3
Others[a]	2	6.3
Initial CA19-9 (IU/ml)	Median 593.89 (8.74–28,494)	

ECOG PS Eastern Cooperative Oncology Group, performance status

[a] Other sites of metastasis include subcutaneous tissue and adrenal gland

Table 2 Drug delivery

Total number of cycles administered	108	
Number of cycles per patient		
Median	2	
Range	1–8	
	Capecitabine	Cisplatin
Relative dose intensity per patient		
Average, %	87.0%	90.8%
75–100%	25 patients (78.1%)	29 patients (90.6%)
<75%	7 patients (21.9%)	3 patients (9.4%)

(range 1–8 cycles). The delivered dose intensities were 87.0% for capecitabine and 90.8% for cisplatin in average. Most patients were treated with more than 75% of relative dose intensity of capecitabine and cisplatin (25/32, 78.1% patients in capecitabine and 29/32, 90.6% patients in cisplatin, respectively). Capecitabine was administered with a reduced dose in 44/108 cycles (40.7%), but cisplatin dose was not reduced in any cycle. Chemotherapy schedule was delayed in 29/108 cycles (26.9%).

Response

Twenty-seven (84.4%) of 32 patients were evaluable for responses. Five patients were not evaluable but were included in the intent-to-treat analysis. Four patients refused further treatment following the first-cycle; three of them were referred to other hospitals for second opinion and one of them wanted to stop chemotherapy due to toxicity, and one patient was lost to follow-up after the first-cycle of chemotherapy. By the intent-to-treat analysis, the overall response rate was 40.6% (95% CI, 23.7–59.4) with 0 CR and 13 PRs (Table 3). Stable disease was observed in 3 patients (9.4%) and 11 patients (34.4%) had progressive disease. The median duration of response in responders was 3.4 months (range 1.3–8.8 months). In 15 patients with gallbladder cancer, 8 patients (53.3%) achieved partial responses and 5 patients (33.3%) showed progressive disease. In 17 patients with intra- or extrahepatic cholangiocarcinoma, 5 patients (29.4%) achieved partial responses with 3 patients (17.6%) of stable disease, and 6 patients (35.3%) had progressive disease. In 13 patients who achieved partial remissions, 8 patients (61.5%) had gall bladder cancer and 5 patients (38.5%) had intra- or extrahepatic cholangiocarcinoma ($P = 0.27$).

Survival

All 32 patients were included in the survival analysis on an intent-to-treat basis. The median time to progression (TTP) was 3.5 months (95% CI, 1.3–5.8, Fig. 1) and the median overall survival (OS) was 12.4 months (95% CI, 6.3–18.5, Fig. 2) after the median follow-up duration of 9.5 months (range 4.8–26.1 months). The median OS in responders has not been reached, and the median TTP in responders was 6.4 months (95% CI, 4.9–7.8). One year survival rate was 54.5%. In patients with gall bladder cancer, median TTP was 4.3 months (95% CI, 2.0–6.6), median survival was not reached yet and 1 year survival rate was 66.0%. In patients with intra- or extrahepatic cholangiocarcinoma, median TTP was 3.0 months (95% CI 0–6.5), median survival was 7.8 months (95% CI, 6.8–8.8) and 1 year survival rate was 42.1%. But there were no statistical differences in OS ($P = 0.22$) and TTP ($P = 0.55$) between patients with gall bladder cancer and cholangiocarcinoma. Between patients with and without

Table 3 Treatment responses

Tumor response	GB cancer (15)	Cholangiocarcinoma (17)	All patients (32)
Complete response	0	0	0
Partial response	8 (53.3%)	5 (29.4%)	13 (40.6%)
Stable disease	0 (0%)	3 (17.6%)	3 (9.4%)
Progressive disease	5 (33.3%)	6 (35.3%)	11 (34.4%)
Not evaluable	2 (13.3%)	3 (17.6%)	5 (15.6%)

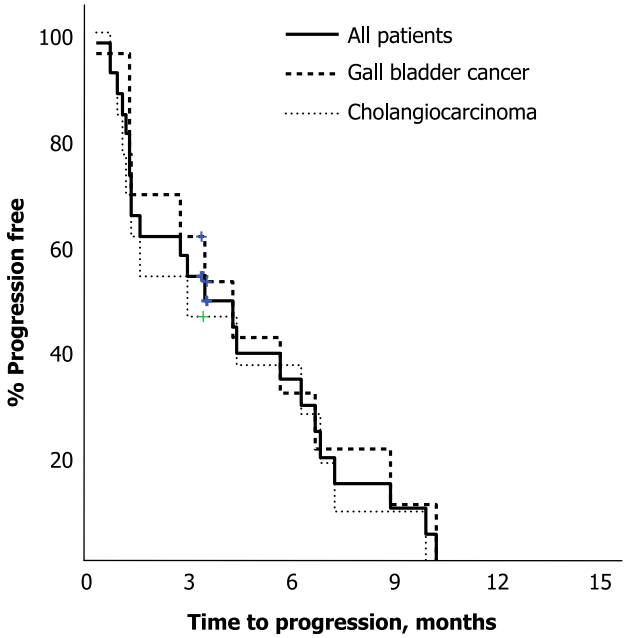

Fig. 1 Time to progression (TTP) of all patients and according to the primary sites. The median TTP of all patients was 3.5 months (95% CI, 1.3–5.8) and 6.4 months in responders especially. The median TTP was 4.3 months (95% CI 2.0–6.6) in patients with gallbladder cancer and 3.0 months (95% CI 0–6.5) in patients with cholangiocarcinoma

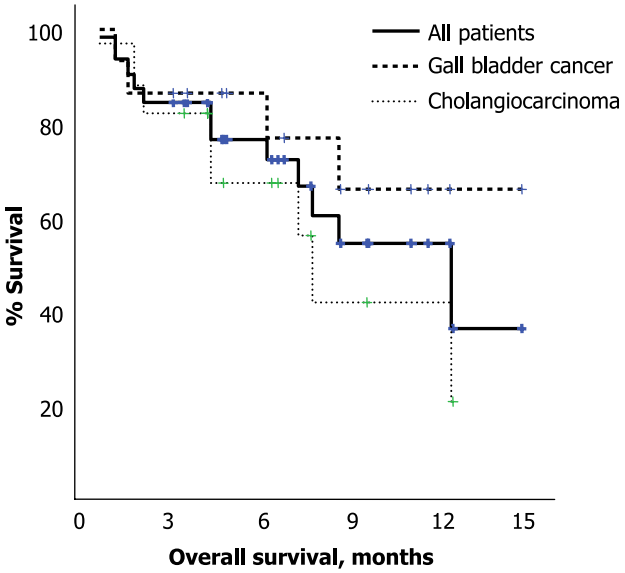

Fig. 2 Overall survival (OS) of all patients and according to the primary sites. The median OS was 12.4 months (95% CI, 6.3–18.5) after the median follow-up duration of 9.5 months (range 4.8–26.1 months). The median OS in responders and patients with gallbladder cancer has not been reached yet, and 7.8 months (95% CI, 6.8–8.8) in patients with cholangiocarcinoma

peritoneal seeding, there was statistical difference in median OS (2.3 vs. 12.4 months, $P = 0.02$), but not in median TTP ($P = 0.14$). Gender, initial disease status, and site of metastasis (liver, lymph nodes, and lung) were not related to the overall survival ($P = 0.25$, 0.47, 0.49, 0.28, and 0.39) and time to progression ($P = 0.55$, 0.93, 0.91, 0.15, and 0.94).

Toxicities

All patients were evaluable for toxicities, and toxicities observed during treatment are listed in Table 4. No NCI-CTC grade 4 toxicity was observed. Grade 3 hematologic toxicities included neutropenia in five patients (15.6%) and eight cycles (7.4%), thrombocytopenia and anemia in one patient (3.1%) and one cycle (0.9%), respectively. No febrile neutropenia was observed. No grade 4 non-hematologic toxicity was observed either. Grade 3 non-hematologic toxicities included hyperbilirubinemia in two patients (6.3%) and two cycles (1.9%), elevation of alkaline phosphatase in two patients (6.3%) and three cycles (2.8%), hand–foot syndrome in two patients (6.3%) and three cycles (2.8%), and anorexia and diarrhea in one patient (3.1%) and one cycle (0.9%), respectively. Grade 2 or 3 hand–foot syndrome occurred in 8 patients (25%) and 15 cycles (13.9%). There was no treatment-related death.

Discussion

To date, in advanced biliary tract cancers, the role of chemotherapy is still to be defined and there is no standard chemotherapeutic regimen. Thus, the regimen mainly consisting of continuous 5-FU was used as standard chemotherapy in combination with platinum or anthracycline [13, 20]. A 5-day continuous infusional

Table 4 Toxicity profile

	Per cycle ($N = 108$)				Per patient ($N = 32$)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicities								
Leukopenia	10 (9.3)	12 (11.1)	–	–	4 (12.5)	8 (25.0)	–	–
Neutropenia	9 (8.3)	15 (13.9)	8 (7.4)	–	2 (6.3)	5 (15.6)	5 (15.6)	–
Febrine neutropenia	–	–	–	–	–	–	–	–
Thrombocytopenia	46 (42.6)	9 (8.3)	1 (0.9)	–	13 (40.6)	4 (12.5)	1 (3.1)	
Anemia	57 (52.8)	21 (19.4)	1 (0.9)	–	22 (68.8)	4 (12.5)	1 (3.1)	–
Non-hematologic toxicities								
Hyperbilirubinemia	6 (5.6)	6 (5.6)	2 (1.9)	–	2 (6.3)	4 (12.5)	2 (6.3)	–
ALP abnormality	32 (29.6)	–	3 (2.8)	–	18 (56.3)		2 (6.3)	–
Anorexia	7 (6.5)	3 (2.8)	1 (0.9)	–	5 (13.9)	5 (13.9)	1 (3.1)	–
Constipation	2 (1.9)	1 (0.8)	–	–	1 (3.1)	1 (3.1)	–	–
Diarrhea	9 (8.3)	3 (2.8)	1 (0.9)	–	7 (21.9)	3 (9.4)	1 (3.1)	–
Stomatitis	10 (9.3)	9 (8.3)	–	–	2 (6.3)	8 (25.0)	–	–
Vomiting	25 (23.1)	5 (4.6)	–	–	11 (34.4)	4 (12.5)	–	–
HFS	22 (20.4)	12 (11.1)	3 (2.8)	–	5 (15.6)	6 (18.8)	2 (6.3)	–
Neuropathy	9 (8.3)	2 (1.9)	–	–	4 (12.5)	2 (6.3)	–	–

5-FU and cisplatin (FP) regimen was reported to achieve a response rate of 24% and the median overall survival of 10 months [13]. FP is one of the most commonly used regimen in upper gastrointestinal tract cancers, such as esophagus and stomach [13, 21, 22], and many trials preferred to deliver 5-FU as continuous infusion because it is thought to be more effective and less toxic compared with bolus injection [23]. But continuous infusion of 5-FU is inconvenient in terms of hospitalization for several days and need of vascular access to central veins frequently. Thus recently, capecitabine is thought to be a substitution for 5-FU because of its mechanism of action. Capecitabine is metabolized to 5-FU by thymidine phosphorylase which is present at higher levels in tumor cells than normal cells [24]. Combination of capecitabine and cisplatin (XP) was proved to be effective and safe in advanced gastric cancer [16], and furthermore some authors reported XP was superior to FP in those patients [17]. This trend of substitution of 5-FU to capecitabine is also found in colorectal cancer and other gastrointestinal malignancies [14, 16, 25, 26]. Kim et al. [27] reported phase II trial of capecitabine and cisplatin in advanced biliary tract cancer in 2003. That trial was same as our trial in design, subjects, dosage, and schedule. They reported 21.4% of overall response rate with 9.1 months of median survival. In our study, overall response rate was 40.6%, median overall survival was 12.4 months (95% CI, 6.3–18.5), and median time to progression was 3.5 months (95% CI, 1.3–5.8). Especially in responders, the median TTP was 6.4 months and the median OS was not reached yet. Our study showed comparable results with previous study in overall response rate (40.6 vs. 21.4%, $P = 0.073$) and overall survival. In patients with gall bladder cancer, 8 patients (53.3%) out of 15 patients responded to treatment in our study, and 6 patients (32%) out of 19 patients responded in previous study ($P = 0.83$). In patients with cholangiocarcinoma, 5/17 patients (29.4%) responded in our study, 3/23 patients (13.0%) responded in a previous study ($P = 0.20$). Pooling of responses in our study and previous study, 22/74 (29.7%) patients with advanced biliary tract cancer responded to chemotherapy of capecitabine and cisplatin, and it could be thought to demonstrate the antitumor activity of this regimen.

In one study, 5-day continuous infusion of 5-FU was associated with high rate of grade 3 or 4 hematologic toxicities (up to 40%), including 17% of febrile neutropenia [13] and in another study with combination of anthracycline, severe grade 4 hematologic toxicities were observed in 32% of patients [20] and also alopecia was frequently observed. In our study, only 8/108 (7.4%) cycles and 5/32 (15.6%) patients had grade 3 neutropenia with no febrile episode, and no alopecia of grade 3 or 4 was observed. This result of isolated neutropenia with no febrile episode is identical to a previous study of this regimen [27]. Hand–foot syndrome, infamous side effect of capecitabine, was observed in 2/32 patients (6.3%) with grade 3 toxicity in our study. In one trial, no large grade 3 hand-foot syndrome was observed with capecitabine, but the dose of capecitabine was half of this study [25], and in another trial which showed only 2% of patients had grade 3 hand-foot syndrome, the dose of capecitabine was less intense than our study [27].

Recently, gemcitabine, which has proven activity in metastatic pancreatic cancer, has been tried to achieve

an efficacy with less toxicities [8, 25, 28–31], and showed response rates of 25–40% approximately. Recent study of gemcitabine and cisplatin for advanced biliary tract cancers showed modest response rates of 34.5% with median overall survival of 10.0 months [28], and another trial showed response rates of 27.5 and 32.5% of stable disease rates [32]. In the latter trial by Thongprasert et al. [32], 39 out of 40 assessable patients had histology of cholangiocarcinoma (97.5%). They showed promising activity of gemcitabine and cisplatin regimen in patients with cholangiocarcinoma.

With an overall response rate of 40.6%, and 9.4% of stable disease in addition, and an tolerable toxicity profiles, the results of this study are comparable with previous trials of this regimen [27, 32] or other regimens before [12, 28–31, 33–37] in this patient population with biliary tract cancers.

New combination regimens and new drugs for biliary tract cancers are emerging recently. Cho et al. reported combination chemotherapy of capecitabine and gemcitabine showed 32% of response rate and 14 months of overall survival [25]. Trials with gemcitabine and oxaliplatin also showed promising activities. Andre et al. [38] reported 36% of response rates and 26% of stable disease rates with OS of 15.4 months. Another trial of gemcitabine and oxaliplatin was performed by Verderame et al. [39] in 2006. They showed 50% response rates, but relatively small number of patients (24 patients) would be a limitation of that study. S-1, a novel orally administered drug of another 5-FU analogue, is a promising agent with antitumor activity in biliary tract cancers. S-1 produced single agent activity with response rate of 21% and favorable toxicity profiles in one trial [37]. This agent is now on several trials in combination with other drugs.

In conclusion, our study indicates that combination chemotherapy with capecitabine and cisplatin is a promising and well-tolerated therapeutic option for the patients with advanced biliary tract cancer. According to recent trials, capecitabine is one of the most studied agent for the biliary tract cancer and might be replaced for continuous 5-FU infusion; thus should be considered as a promising therapeutic option in the treatment of biliary tract cancer.

References

1. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ (2003) Cancer statistics. CA Cancer J Clin 53:5–26
2. Patel T (2002) Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2:10
3. Faivre J, Forman D, Esteve J, Obradovic M, Sant M (1998) Survival of patients with primary liver cancer, pancreatic cancer and biliary tract cancer in Europe. EUROCARE Working Group. Eur J Cancer 34:2184–2190
4. Shin HRJK, Won YJ, Park JG, 139 KCCR-affiliated Hospitals (2004) 2002 annual report of the Korea Central Cancer Registry. Cancer Res Treat 36:103–114
5. Hirono S, Tani M, Kawai M, Ina S, Uchiyama K, Yamaue H (2006) Indication of hepatopancreatoduodenectomy for biliary tract cancer (discussion 574–565). World J Surg 30:567–573
6. Jarnagin WR (2000) Cholangiocarcinoma of the extrahepatic bile ducts. Semin Surg Oncol 19:156–176
7. Pichlmayr R, Lamesch P, Weimann A, Tusch G, Ringe B (1995) Surgical treatment of cholangiocellular carcinoma. World J Surg 19:83–88
8. Alberts SR, Al-Khatib H, Mahoney MR, Burgart L, Cera PJ, Flynn PJ, Finch TR, Levitt R, Windschitl HE, Knost JA, Tschetter LK (2005) Gemcitabine, 5-fluorouracil, and leucovorin in advanced biliary tract and gallbladder carcinoma: a North Central Cancer Treatment Group phase II trial. Cancer 103:111–118
9. Colleoni M, Di Bartolomeo M, Di Leo A, Zilembo N, Carnaghi C, Pandolfi A, Rimassa L, Artale S, Bajetta E (1995) Oral chemotherapy with doxifluridine and folinic acid in biliary tract cancer. Eur J Cancer 31A:2426–2427
10. Eckel F, Lersch C, Assmann G, Schulte-Frohlinde E (2000) Phase II trial of low-dose cyclophosphamide, leucovorin, high-dose 5-fluorouracil 24-hour continuous infusion and tamoxifen in advanced biliary tract cancer. Ann Oncol 11:762–763
11. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, Shimma N, Umeda I, Ishitsuka H (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
12. Patt YZ, Hassan MM, Lozano RD, Waugh KA, Hoque AM, Frome AI, Lahoti S, Ellis L, Vauthey JN, Curley SA, Schnirer II,Raijman I (2001) Phase II trial of cisplatin, interferon alpha-2b, doxorubicin, and 5-fluorouracil for biliary tract cancer. Clin Cancer Res 7:3375–3380
13. Ducreux M, Rougier P, Fandi A, Clavero-Fabri MC, Villing AL, Fassone F, Fandi L, Zarba J, Armand JP (1998) Effective treatment of advanced biliary tract carcinoma using 5-fluorouracil continuous infusion with cisplatin. Ann Oncol 9:653–656
14. Patt YZ, Hassan MM, Aguayo A, Nooka AK, Lozano RD, Curley SA, Vauthey JN, Ellis LM, Schnirer II, Wolff RA, Charnsangavej C, Brown TD (2004) Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 101:578–586
15. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, Bugat R, Burger U, Garin A, Graeven U, McKendric J, Maroun J, Marshall J, Osterwalder B, Perez-Manga G, Rosso R, Rougier P, Schilsky RL (2002) First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 13:566–575
16. Kang HJ, Chang HM, Kim TW, Ryu MH, Sohn HJ, Yook JH, Oh ST, Kim BS, Lee JS, Kang YK (2005) Phase II study of capecitabine and cisplatin as first-line combination therapy in patients with gastric cancer recurrent after fluoropyrimidine-based adjuvant chemotherapy. Br J Cancer 92:246–251
17. Y. Kang WKK, Shin DB, Chen J, Xiong J, Wang J, Lichinitser M, Philco M, Suarez T, Santamaria J (2006) Randomized phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients

(pts) with advanced gastric cancer (AGC): efficacy and safety results. J Clin Oncol (Meeting Abstracts) 24
18. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
19. Anderson JR, Bernstein L,Pike MC (1982) Approximate confidence intervals for probabilities of survival and quantiles in life-table analysis. Biometrics 38:407–416
20. Ellis PA, Norman A, Hill A, O'Brien ME, Nicolson M, Hickish T,Cunningham D (1995) Epirubicin, cisplatin and infusional 5-fluorouracil (5-FU) (ECF) in hepatobiliary tumours. Eur J Cancer 31A:1594–1598
21. De Besi P, Sileni VC, Salvagno L, Tremolada C, Cartei G, Fosser V, Paccagnella A, Peracchia A,Fiorentino M (1986) Phase II study of cisplatin, 5-FU, and allopurinol in advanced esophageal cancer. Cancer Treat Rep 70:909–910
22. Kang ea (2006) Randomized phase III trial of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients (pts) with advanced gastric cancer (AGC): Efficacy and safety results. J Clin Oncol (Meeting Abstracts) 24
23. Weinerman B, Shah A, Fields A, Cripps IC, Wilson K, McCormick R, Temple W, Maroun J, Bogues W, Pater J et al (1992) Systemic infusion versus bolus chemotherapy with 5-fluorouracil in measurable metastatic colorectal cancer. Am J Clin Oncol 15:518–523
24. Walko CM,Lindley C (2005) Capecitabine: a review. Clin Ther 27:23–44
25. Cho JY, Paik YH, Chang YS, Lee SJ, Lee DK, Song SY, Chung JB, Park MS, Yu JS, Yoon DS (2005) Capecitabine combined with gemcitabine (CapGem) as first-line treatment in patients with advanced/metastatic biliary tract carcinoma. Cancer 104:2753–2758
26. Rich T (2002) Capecitabine and radiation therapy for advanced gastrointestinal malignancies. Oncology (Williston Park) 16:27–30
27. Kim TW, Chang HM, Kang HJ, Lee JR, Ryu MH, Ahn JH, Kim JH, Lee JS, Kang YK (2003) Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced biliary cancer. Ann Oncol 14:1115–1120
28. Kim ST, Park JO, Lee J, Lee KT, Lee JK, Choi SH, Heo JS, Park YS, Kang WK, Park K (2006) A Phase II study of gemcitabine and cisplatin in advanced biliary tract cancer. Cancer 106:1339–1346
29. Murad AM, Guimaraes RC, Aragao BC, Rodrigues VH, Scalabrini-Neto AO, Padua CA, Moore FC (2003) Phase II trial of the use of gemcitabine and 5-fluorouracil in the treatment of advanced pancreatic and biliary tract cancer. Am J Clin Oncol 26:151–154
30. Penz M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger W, Lenauer A, Depisch D, Krauss G, Schneeweiss B, Scheithauer W (2001) Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 12:183–186
31. Tsavaris N, Kosmas C, Gouveris P, Gennatas K, Polyzos A, Mouratidou D, Tsipras H, Margaris H, Papastratis G, Tzima E, Papadoniou N, Karatzas G,Papalambros E (2004) Weekly gemcitabine for the treatment of biliary tract and gallbladder cancer. Invest New Drugs 22:193–198
32. Thongprasert S, Napapan S, Charoentum C,Moonprakan S (2005) Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. Ann Oncol 16:279–281
33. Cho JY, Nam JS, Park MS, Yu JS, Paik YH, Lee SJ, Lee DK,Yoon DS (2005b) A Phase II study of capecitabine combined with gemcitabine in patients with advanced gallbladder carcinoma. Yonsei Med J 46:526–531
34. Kornek GV, Schuell B, Laengle F, Gruenberger T, Penz M, Karall K, Depisch D, Lang F,Scheithauer W (2004) Mitomycin C in combination with capecitabine or biweekly high-dose gemcitabine in patients with advanced biliary tract cancer: a randomised phase II trial. Ann Oncol 15:478–483
35. Okusaka T, Ishii H, Funakoshi A, Yamao K, Ohkawa S, Saito S, Saito H,Tsuyuguchi T (2006) Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer. Cancer Chemother Pharmacol 57:647–653
36. Park SH, Park YH, Lee JN, Bang SM, Cho EK, Shin DB,Lee JH (2006) Phase II study of epirubicin, cisplatin, and capecitabine for advanced biliary tract adenocarcinoma. Cancer 106:361–365
37. Ueno H, Okusaka T, Ikeda M, Takezako Y,Morizane C (2004) Phase II study of S-1 in patients with advanced biliary tract cancer. Br J Cancer 91:1769–1774
38. Andre T, Tournigand C, Rosmorduc O, Provent S, Maindrault-Goebel F, Avenin D, Selle F, Paye F, Hannoun L, Houry S, Gayet B, Lotz JP, de Gramont A,Louvet C (2004) Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 15:1339–1343
39. Verderame F, Russo A, Di Leo R, Badalamenti G, Santangelo D, Cicero G, Valerio MR, Gulotta G, Tomasello G, Gebbia N,Fulfaro F (2006) Gemcitabine and oxaliplatin combination chemotherapy in advanced biliary tract cancers. Ann Oncol 17:vii68–vii72