Capecitabine Combined with Gemcitabine (CapGem) as First-Line Treatment in Patients with Advanced/Metastatic Biliary Tract Carcinoma

Jae Yong Cho, M.D., Ph.D.[1]
Yong Han Paik, M.D., Ph.D.[1]
Yoon Soo Chang, M.D., Ph.D.[1]
Se Joon Lee, M.D.[1]
Dong-Ki Lee, M.D., Ph.D.[1]
Si Young Song, M.D., Ph.D.[1]
Jae Bock Chung, M.D., Ph.D.[1]
Mi-Suk Park, M.D.[2]
Jeong-Sik Yu, M.D.[2]
Dong-Sup Yoon, M.D., Ph.D.[3]

[1] Department of Internal Medicine, Yongdong Severance Hospital Pancreatobiliary Clinic, Yonsei University College of Medicine, Seoul, South Korea.

[2] Department of Diagnostic Radiology, Yongdong Severance Hospital Pancreatobiliary Clinic, Yonsei University College of Medicine, Seoul, South Korea.

[3] Department of Surgery, Yongdong Severance Hospital Pancreatobiliary Clinic, Yonsei University College of Medicine, Seoul, South Korea.

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Address for reprints: Jae Yong Cho, M.D., Ph.D., Yongdong Severance Hospital, Yonsei University Medical College, Do-gok Dong, Kang-nam Gu, Seoul, South Korea; Fax: (011) 82-2-3463-3882; E-mail: chojy@yumc.yonsei.ac.kr

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BACKGROUND. Biliary tract carcinoma is an aggressive cancer, with median survival rarely exceeding 6 months. There is currently no established palliative standard of care. A Phase II trial was conducted to study a combination of oral capecitabine and gemcitabine (CapGem) as first-line therapy in patients with advanced and/or metastatic biliary carcinoma.

METHODS. Patients with unresectable or metastatic intrahepatic or extrahepatic biliary duct carcinoma and gallbladder carcinoma were enrolled. Eligible patients had histologically or cytologically confirmed, measurable adenocarcinoma and had not received prior therapy with capecitabine or gemcitabine. Treatment consisted of intravenous (i.v.) gemcitabine (1000 mg/m^2 on Days 1 and 8) plus oral capecitabine (650 mg/m^2 twice daily on Days 1–14) every 3 weeks for up to 6 cycles. Tumor response, survival, and safety were determined.

RESULTS. A total of 44 patients were evaluable. Primary tumor sites were: intrahepatic (n = 14) and extrahepatic biliary duct (n = 16); gallbladder (n = 7); and ampulla (n = 7). Fourteen (32%) patients had a partial response and 15 (34%) patients had stable disease. Median time to disease progression and overall survival were 6.0 (range, 3.8–8.1) and 14 (range, 11.4–16.6) months, respectively. The 1-year survival rate was 58%. No Grade 4 adverse events were seen. Transient Grade 3 neutropenia/thrombocytopenia and manageable (almost invariably Grade 2) nausea, diarrhea, and hand–foot syndrome were the most common adverse events.

CONCLUSIONS. CapGem is an active and well tolerated first-line combination chemotherapy regimen for patients with advanced/metastatic biliary tract carcinoma that offers a convenient home-based therapy. ***Cancer* 2005;104:2753–8.**

KEYWORDS: biliary tract carcinoma, Phase II trial, capecitabine, gemcitabine.

Biliary tract carcinomas are aggressive tumors with a poor prognosis. While surgical resection of the primary tumor and the areas of local extension remains the most effective therapy, <25% of patients will be resectable at presentation.[1–4] The remaining 75% will receive palliative therapy, with a median survival of approximately 6 months. In addition, those undergoing potentially curative resections experience high rates of disease recurrence and are generally incurable at recurrence. To date, chemotherapy has had limited impact on this disease, because of the absence of agents with substantial activity in these tumors and the overall morbidity of this patient population.

5-Fluorouracil (5-FU) has been considered the mainstay of palliative chemotherapy; however, response rates from Phase III trials are in the range of 0–10%.[5,6] Continuous infusion of 5-FU offers

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several potential advantages over intravenous (i.v.) bolus administration, but impracticality limits its use. Capecitabine (Xeloda, Hoffman La Roche, Nutley, NJ) is an oral fluoropyrimidine that generates 5-FU selectively in tumor tissues. This selectivity is achieved by the enzyme thymidine phosphorylase (TP), which is responsible for the final conversion of capecitabine to 5-FU and is found at much higher levels in tumors compared with normal tissues.[7–10] Capecitabine offers the possibility of continuous tumor exposure to 5-FU by preferential activation at the tumor site, while minimizing the potential exposure of healthy body tissues to systemic 5-FU.

The nucleoside analog gemcitabine has shown single-agent activity in Phase II trials in biliary tract carcinoma with response rates ranging from 8–36%.[11–15] Gemcitabine and 5-FU in combination appear to have synergy in preclinical studies.[16] A Phase I–II trial by Hidalgo et al.,[17] evaluating 5-FU administered in a protracted i.v. infusion plus weekly gemcitabine in patients with pancreatic carcinoma, showed promising activity. Other than the dose-limiting toxicities of neutropenia or thrombocytopenia, the regimen was well tolerated. On the basis of these findings, the combination of capecitabine and gemcitabine (CapGem) warrants investigation for the treatment of biliary tract carcinoma. The present study was designed to evaluate CapGem activity and tolerability in patients with advanced/metastatic biliary tract carcinoma.

MATERIALS AND METHODS

The study recruited patients between January 2001 and June 2003. Eligible patients were between 18 and 75 years of age and had histologically or pathologically confirmed advanced or metastatic, bidimensionally measurable biliary tract carcinoma not amenable to curative surgery (WHO criteria). Patients had not previously received chemotherapy for their disease. Patients were required to have a Karnofsky Performance Status (KPS) $\geq$70%, adequate renal, hepatic, and hematologic functions, and a life expectancy of $>$3 months. Serum bilirubin was up to 3$\times$ the upper limit of normal. A detailed medical history, physical and neurologic examinations, chest X-ray, spiral computed tomographic (CT) scan of the abdomen, and ECG were performed within the 2 weeks before study commencement. Run-in procedures, including vital signs and clinical laboratory tests, were performed within 7 days before the start of chemotherapy. All patients gave written informed consent to participate. The trial protocol received local ethical board approval and the study was conducted according to the principles of the Declaration of Helsinki and its subsequent amendments.

Treatment and Dose Modifications

Most (82%) patients were treated on an outpatient basis. Gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) was given as a 30-minute i.v. infusion on Days 1 and 8 of each cycle at a dose of 1000 mg/m^2. Capecitabine (Xeloda, Hoffman La Roche) was administered orally at a dose of 650 mg/m^2 twice daily on Days 1–14 followed by 1 week of rest. Cycles were repeated every 3 weeks unless patients experienced treatment-related adverse effects. Standard antiemetic treatment with granisetron or ondansetron was administered to all patients. Prophylactic administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not allowed. Treatment was administered for at least six cycles or until disease progression, at the physicians' discretion. Dose adjustment criteria were based on hematologic parameters. For Grade 3/4 afebrile neutropenia, subsequent cycles were repeated with rhG-CSF prophylactic administration. In cases of febrile neutropenia or Grade 3/4 neutropenia despite the prophylactic administration of rhG-CSF, gemcitabine and capecitabine doses were each reduced by 25%. For Grade 3/4 thrombocytopenia lasting $>$5 days, doses of both drugs were reduced by 25%. The dose of capecitabine was reduced by 25% in case of Grade 3/4 diarrhea or hand–foot syndrome (HFS).

Patients with complete remission (CR), partial remission (PR), or stable disease (SD), and who were tolerating treatment well, were treated for up to six cycles. Those with clearly documented progressive disease (PD) were taken off treatment at the time of progression. Responding patients (CR or PR) or those with SD after 18 weeks were followed until PD and were able to continue on CapGem at the discretion of the investigator.

Efficacy

Tumor assessments, according to WHO criteria,[18] were performed at 6-week intervals by the investigators. Tumor lesions were assessed by CT scan, X-rays, or magnetic resonance imaging (MRI), and objective tumor response was based on the dimensions of measurable marker lesions, measured by the same radiologist throughout the study. Tumor response was also determined by an Independent Review Committee (IRC). Time to disease progression (TTP) was calculated as the time from first treatment to the time the patient was first recorded as having 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

Safety was monitored throughout the study and for 28 days after the last study treatment. Adverse events were graded according to the National Cancer Institute–Common Toxicity Criteria (NCI-CTC). HFS was graded as in previous capecitabine studies.[19] Patients were educated to recognize adverse effects ≥Grade 2 and interrupted capecitabine until further instructed by their physician.

Statistics

The response rate was expected to be approximately 25%; a sample size of 38 was calculated by Fleming single-stage design[20] to ensure at least 80% power for proving lack of efficacy if the true response rate was less than 25%. Estimating a dropout rate of 15%, a total of 44 patients were recruited to ensure that at least 38 patients were evaluable. TTP and survival were analyzed by the Kaplan–Meier product limit method. Patients who received at least one dose of study medication were included in the intention-to-treat (ITT) analysis. Those who did not receive at least one dose of study medication or for whom no follow-up safety information was available were excluded from the safety analysis.

RESULTS

Patient Characteristics

Of the 45 patients enrolled, 44 (26 women and 18 men) received at least one dose of CapGem and were evaluable for efficacy and safety (ITT population). One patient withdrew consent during the screening period and did not receive CapGem. As shown in Table 1, the majority of patients (77%) had Stage IV disease and the most commonly affected metastatic sites were the liver (52%) and lymph nodes (45%). Thirty-two percent of patients had undergone one or more type of surgical intervention for their cancer.

TABLE 1
Baseline Patient and Disease Characteristics (n = 44 Patients)

Characteristic	Value (%)
Age (yrs)	
Median	62
Range	41–75
Gender (no. of patients)	
Male	18 (41)
Female	26 (59)
Karnofsky Performance status, %	
Median	90
Range	70–100
Disease stage, no. of patients	
Locally advance	10 (23)
Metastatic	34 (77)
Primary tumor site, no. of patients	
Intrahepatic bile ducts	14 (32)
Extrahepatic bile ducts	16 (36)
Gallbladder	7 (16)
Ampulla	7 (16)
Location of metastatic sites	
Liver	23 (52)
Lymph nodes	20 (45)
Lung	9 (20)
Bone	6 (14)
Other	4 ((9)
Patients with ≥1 surgical intervention	10 (23)

TABLE 2
Antitumor Activity (ITT Analysis; n = 44)

Response (investigator assessment)	No.	% (95% CI)
Overall response	14	32 (19–48)
Complete response	0	0
Partial response	14	32 (19–48)
Stable disease	15	34 (20–50)
Progressive disease	15	34 (20–50)

ITT, intention to treat.

Efficacy

Response data according to the investigator assessment are summarized in Table 2. The objective response rate (ORR) was 32% (95% confidence interval [CI]: 19–48%), all of which were PRs (n = 14). The same ORR was confirmed by the IRC. According to the investigators, 15 (34%) patients had SD. IRC confirmed 13 (30%) patients with SD. For patients with gallbladder carcinoma (n = 7), ORR was 57%. For patients with intrahepatic (n = 14) and extrahepatic (n = 16) bile duct and ampulla (n = 7) carcinoma, ORRs were 36%, 25%, and 29%, respectively.

The median TTP was 6.0 months (95% CI: 3.0–8.1 mos, Fig. 1) and the median overall survival (OS) was 14 months (95% CI: 11.4–16.6 mos, Fig. 2). The 1-year actuarial survival rate was 58%.

The median duration of treatment for all patients was 63 days (range, 7–238 days). Eighteen (41%) patients were treated for at least 18 weeks; of these, 10 (23%) were treated for more than 18 weeks in the continuation phase.

Safety

Nonhematologic adverse events are summarized in Figure 3. Grade 2/3 nonhematologic adverse events were: nausea (12/2%), HFS (9/0%), vomiting (8/3%), constipation (5/2%), anorexia (3/2%), general weakness (3/0%), insomnia (2/0%), and diarrhea (2/0%). Hematologic adverse events are summarized in Figure

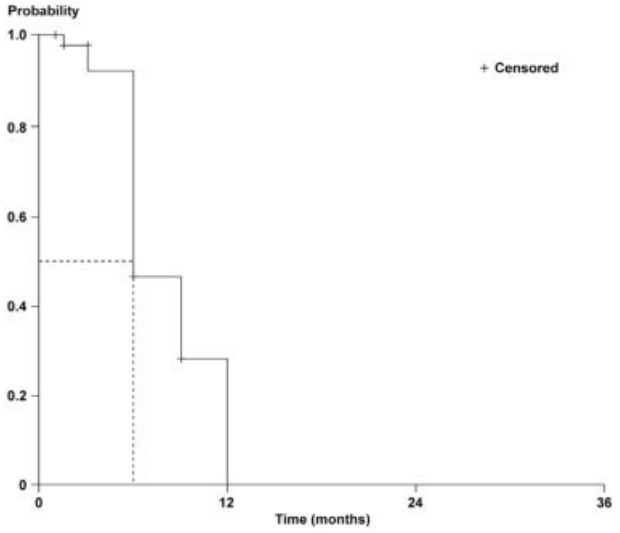

FIGURE 1. Time to disease progression.

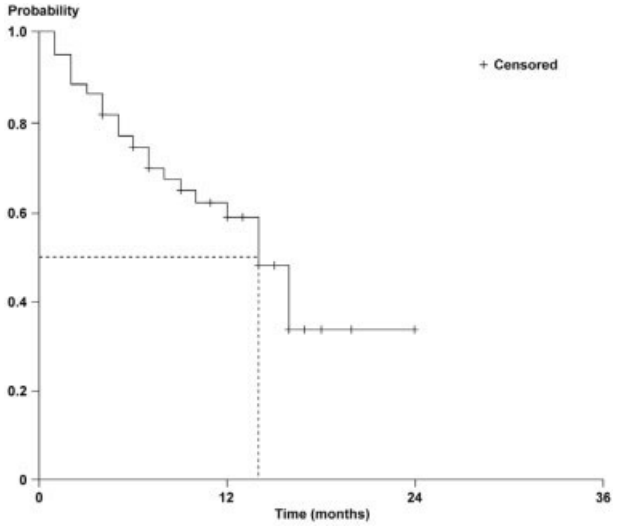

FIGURE 2. Overall survival.

4. Grade 3 neutropenia and Grade 3 thrombocytopenia occurred in 11% and 9% of patients, respectively. Three patients developed febrile episodes. No Grade 4 nonhematologic or hematologic adverse events were seen. No patient discontinued treatment because of abnormal laboratory values. No deaths attributable to adverse events occurred during the study. There were 23 deaths reported during the study, the majority of which occurred more than 28 days after the end of the planned treatment schedule. All of the deaths were related to PD.

A median of four courses of treatment (range, 1–16 courses of treatment) were given. During Cycle 1, 97% (range, 86–100%) and 99% (range, 87–100%) of the planned doses of capecitabine and gemcitabine,

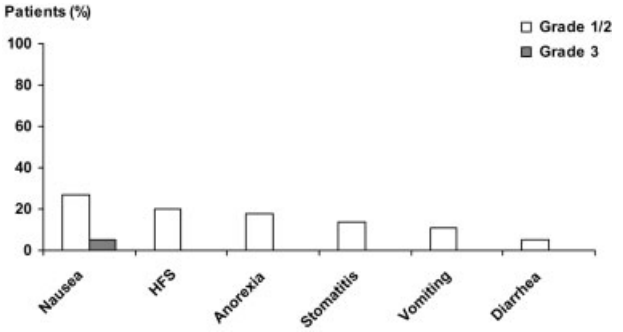

FIGURE 3. Nonhematologic adverse events.

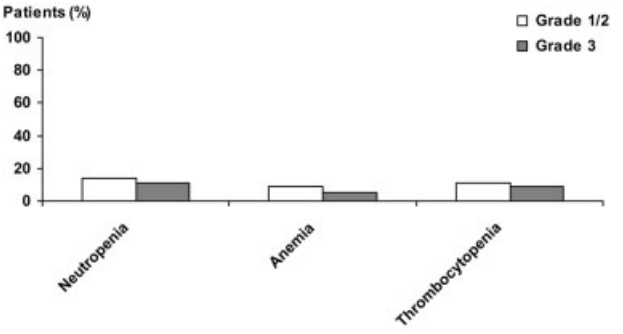

FIGURE 4. Hematologic adverse events.

respectively, were given. During Cycle 2, the corresponding values for capecitabine and gemcitabine were 95% (range, 83–100%) and 96% (range, 85–100%), respectively. Despite the need for dose modifications, 90% of patients received all 3 weeks of treatment with both drugs during the first two cycles of therapy.

DISCUSSION

The current findings show that CapGem combination chemotherapy is active and very well tolerated as a first-line treatment in patients with advanced and/or metastatic biliary tract carcinoma. The ORR was 32% and an additional 30% of patients had durable SD. This compares favorably with results previously reported for 5-FU/gemcitabine combinations in patients with advanced biliary tract carcinoma. Recently, Knox et al.[21] evaluated continuous i.v. infusion of 5-FU (200 mg/m^2 for 21 days) plus gemcitabine (900 mg/m^2 on Days 1, 8, and 15) every 4 weeks in 27 patients with advanced biliary tract adenocarcinoma: ORR was 33% and 30% of patients achieved SD. Gebbia et al.[22] treated 22 biliary carcinoma patients with a combination of gemcitabine (1000 mg/m^2 on Days 1 and 8) and 5-FU (400 mg/m^2 i.v. bolus followed by 600 mg/m^2 by 22-hr continuous i.v. infusion)/leucovorin (100 mg/m^2 i.v. for 2 hr) every 3 weeks: ORR was 36%

and 23% achieved SD. Adverse events were mild in both these studies and similar to our results.

The usual limitations of cross-study comparisons should be taken into account when interpreting efficacy results. However, it is interesting to note that the ORR was better in the present study than the 21% observed in 38 Korean patients with advanced biliary carcinoma receiving capecitabine (1250 mg/m^2 twice daily on Days 1–14) plus cisplatin (60 mg/m^2 on Day 1) every 3 weeks[23] and the 24% observed in 25 French patients with advanced/metastatic biliary carcinoma who were treated with continuous i.v. infusion of 5-FU (1000 mg/m^2/day for 5 days) plus cisplatin (100 mg/m^2 on Day 2) every 3 weeks.[24]

Interpretation of survival data in such relatively small groups of patients is difficult because of potential selection bias. Nonetheless, the median TTP (6 mos) and OS (14 mos) for patients receiving CapGem in the current study is comparable to median TTP and OS (5.7 and 15.4 mos, respectively) previously reported by Andre et al.[25] on behalf of the GERCOR group, who treated 33 patients with advanced biliary adenocarcinoma and achieved good performance status using GEMOX: gemcitabine (1000 mg/m^2 on Day 1) plus oxaliplatin (100 mg/m^2 on Day 2) every 2 weeks. However, larger randomized trials are required to confirm the comparability of these findings.

In addition to antitumor efficacy, safety and convenience are critically important issues for the choice of new treatment combinations. The current CapGem regimen has the advantage over continuous i.v. 5-FU plus either gemcitabine or cisplatin of convenience and practicability, and has clear potential to reduce healthcare resource expenditure. This is because capecitabine is administered orally and avoids the complications related to use of an implanted catheter required for the continuous i.v. administration of 5-FU. Rates of venous thrombosis and central line infection were 7% and 9%, respectively, in the study by Knox et al.,[21] which combined continuous i.v. infusion of 5-FU plus gemcitabine: this complication accounted for almost half of the treatment-related serious adverse events with 5-FU/gemcitabine. Toxicity has been a significant problem with different schedules of 5-FU/cisplatin regimes and needs to be improved. One of the better-tolerated 5-FU plus cisplatin regimens was reported by Taieb et al.,[26] who incorporated the de Gramont 5-FU regimen (5-FU 400 mg/m^2 i.v. bolus followed 22-hr continuous i.v. infusion of 600 mg/m^2 on 2 consecutive days) with a modest dose of cisplatin (50 mg/m^2 on Day 2). They treated 29 patients with advanced/metastatic biliary carcinoma. The ORR was 34%, which is comparable to our result. However, more Grade 3/4 hematologic toxicity (41%) was reported, compared with the rate of 11% seen in our study. Median OS was 9.5 months, which is inferior to our findings (14 mos), although it is difficult to compare survival between single-arm studies.

Biliary tumors can occur anywhere in the hepatobiliary system and are often classified according to location. In the present study, gallbladder carcinoma appeared to respond better than cholangiocarcinoma, although response rates did not differ statistically, possibly because of the relatively small number of patients included in the study. The response rates according to primary site in the present study are in line with those previously mentioned in a GERCOR group study with GEMOX.[25] However, it is important to note that cholangiocarcinoma in this study had more extensive disease than those with gallbladder carcinoma. Further study will be needed to clarify response to chemotherapy according to primary tumor sites.

In conclusion, the CapGem combination is active as a first-line chemotherapy in patients with advanced and/or metastatic biliary tract carcinoma. In this population, a favorable toxicity profile is of great importance, and our study indicated that CapGem was well tolerated. The convenience of administration of the CapGem combination needs to be stressed, as it permits home-based therapy. A confirmatory Phase II study will be needed to validate these promising results with CapGem in this setting.

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