Phase II trial of oxaliplatin combined with leucovorin and fluorouracil for recurrent/metastatic biliary tract carcinoma

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Biliary tract carcinoma is often diagnosed at an advanced stage, and there is currently no established palliative standard of care. This phase II study investigated the efficacy and safety of combination chemotherapy of oxaliplatin, leucovorin, and 5-fluorouracil (5-FU) in biliary tract carcinoma. Patients with unresectable or recurrent biliary tract carcinoma were enrolled, including pretreated and chemotherapy-naive patients. Treatment consisted of intravenous oxaliplatin (100 mg/m^2, day 1) followed by leucovorin (100 mg/m^2, day 1) and 5-FU (1000 mg/m^2, days 1 and 2). Treatment was repeated every 3 weeks. The efficacy and safety of the treatment were determined. Twenty-eight patients were evaluable, and a total of 166 cycles were administered (median five cycles). One complete response (3.6%) and five partial responses (17.9%) were noted, with a response rate of 21.5% [95% confidence interval (CI): 6.2–36.7], according to Response Evaluation Criteria in Solid Tumors criteria. The median time to progression and overall survival was 3.5 months (95% CI: 2.7–4.3) and 10.0 months (95% CI: 7.2–12.8), respectively. The 1-year survival rate was 17.8%. Grade 3/4 neutropenia and thrombocytopenia were recorded in 18 and 4% of the patients, respectively. No treatment-related death was observed. Oxaliplatin in combination with leucovorin and 5-FU should be considered a feasible chemotherapy regimen for patients with recurrent/metastatic biliary tract carcinoma. ***Anti-Cancer Drugs*** **19:631–635 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Biliary tract carcinoma is a rare disease, accounting for less than 1% of cancer deaths in Western countries every year. It is aggressive, however, and has a poor prognosis. As it lacks early symptoms, biliary tract carcinoma is often diagnosed at an advanced/metastatic stage. Although surgical resection of the primary tumor and the areas of local extension remains the most effective therapy, less than 25% of patients are resectable at presentation and relapse rates are high [1–3]. The remaining 75% of patients receive palliative therapy, with a median survival of generally less than 1 year [4]. Postdiagnosis, these highly lethal cancers have 1-year and 2-year survival rates of 25 and 13%, respectively [5]. Chemotherapy improves survival and quality of life in patients with advanced biliary tract carcinoma [6], although no standard chemotherapy regimens have been established.

To date, only small-scale, mostly uncontrolled, studies have been conducted to evaluate many chemotherapy regimens. These studies, however, have reported poor outcome. According to these studies, the overall response rates (RRs) of single-agent or combination therapy [e.g. 5-fluorouracil (5-FU), mitomycin C, cisplatin, etoposide, methotrexate, doxorubicin, irinotecan, and paclitaxel] ranged between only 0 and 20% [7]. Recently, gemcitabine has shown encouraging efficacy and survival rates compared with conventional chemotherapies in advanced biliary tract cancer [8–10]. 5-FU or gemcitabine is widely recommended based on small and predominately phase II trials [11].

Oxaliplatin is a diaminocyclohexane platinum compound, and has an oxalate ligand as the leaving group and a trans-1,2-diaminocyclohexane as the transport ligand [12]. Like cisplatin, oxaliplatin acts as an alkylating cytotoxic agent. Oxaliplatin's diaminocyclohexane platinum adducts, however, seem to be more effective and more cytotoxic than cisplatin adducts with regard to the inhibition of DNA synthesis, because of differences in their targets and mechanisms of action [13]. Combination therapies of cisplatin have shown activity in biliary tract cancer [14,15]. In addition to efficacy of oxaliplatin, the superiority of toxicity profiles of oxaliplatin compared with cisplatin justified the application of oxaliplatin to biliary tract cancer. The combination therapy of oxaliplatin, leucovorin, and 5-FU already showed clinical benefit in

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patients with colorectal cancer [16], gastric cancer [17], and pancreatic cancer [18].

In advanced biliary tract cancer, oxaliplatin monotherapy and combination therapy with 5-FU have also demonstrated promising results [19,20]. Further clinical evidence is still needed, however. So, we planned to evaluate the efficacy and safety of the combination therapy of oxaliplatin (100 mg/m^2), leucovorin (100 mg/m^2), and 5-FU (2000 mg/m^2 for 2 days) for patients with biliary tract carcinoma. The patients with advanced biliary tract carcinoma were generally older and poor in performance, and pretreated patients were also included in this study. Considering patients' tolerability and safety, the chemotherapy was planned to be administered every 3 weeks instead of commonly performed biweekly schedule.

Materials and methods

Eligibility

The eligibility criteria were as follows: (i) histopathologic and/or radiologic evidence of biliary tract carcinoma; (ii) unresectable, locally advanced, metastatic or recurred biliary tract carcinoma; (iii) earlier treatment was allowed if the patient progressed after earlier treatment, either chemotherapy-naive or having completed earlier chemotherapy regimen 3 weeks before entry; (iv) age between 18 and 75 years; (v) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2; (vi) a life expectancy of above or equal to 3 months; (vii) the presence of measurable lesion according to Response Evaluation Criteria in Solid Tumors; and (viii) adequate organ and marrow function [serum creatinine $< 1.5 \times$ upper limit of normal (ULN), serum transaminase $< 2 \times$ ULN, bilirubin $< 2 \times$ ULN, absolute neutrophil count $\geq 1500/\mu l$, platelet count $\geq 100\,000/\mu l$]. Patients were excluded from the study if they had concurrent cancer, peripheral neuropathy of the National Cancer Institute Common Toxicity Criteria grade ≥ 2, brain metastasis, prior use of oxaliplatin, or an uncontrolled significant comorbid condition. The protocol was approved by the Institutional Review Board of Yonsei University Medical Center. All patients provided written informed consent.

Treatment and dose modification

On day 1, patients were given a 2-h intravenous infusion of oxaliplatin 100 mg/m^2, dissolved in a 500-ml dextrose solution, which was followed by leucovorin 100 mg/m^2 intravenous bolus. On days 1 and 2, patients were also given a 24-h intravenous infusion of 5-FU 1000 mg/m^2. Treatment was repeated in 3-week cycles until the occurrence of unacceptable treatment-related adverse events, disease progression, or withdrawal of patient consent. Patients were not allowed to receive prophylactic administration of recombinant human granulocyte colony stimulating factor (G-CSF). In cases of grade 3/4 neutropenia, G-CSF was administered therapeutically. Patients did not begin a new cycle of treatment unless the absolute neutrophil count was $\geq 1500/\mu l$, the platelet count was $\geq 100\,000/\mu l$, and all relevant nonhematological toxicities were below or equal to grade 1. The maximum permissible duration of treatment delay was 3 weeks. If recovery from toxicity did not occur after a delay of 21 days, the patient was withdrawn from the protocol. In cases of febrile neutropenia, grade 3/4 neutropenia, grade 3/4 thrombocytopenia, and above or equal to grade 3 nonhematologic toxicities, oxaliplatin doses were reduced by 15%. Dose reduction was not planned with leucovorin or 5-FU infusion.

Patient evaluation

Baseline evaluation of each patient included a complete medical history, physical examination, complete blood count with differential, serum chemistries with electrolytes, tumor markers, and urine analysis. Physical examination, performance status, complete blood count, and serum chemistries were evaluated before each subsequent cycle. Tumor assessment was performed for every two cycles of chemotherapy, or earlier when indicated clinically. A measurable lesion was defined as ≥ 10 mm measured in any one dimension on a spiral computed tomography scan. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors guidelines [21]. All patients were analyzed as the intention-to-treat analysis. All adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Statistical method

Overall survival (OS) was defined as the interval between the first chemotherapy treatment to death or the last follow-up. Time to progression (TTP) was defined as the time elapsed from the first chemotherapy treatment to disease progression or the date of death if the patient died before progressive disease was demonstrated. TTP and survival were analyzed by the Kaplan–Meier method with a log-rank test. The χ^2 and Fisher's exact tests were used to compare percentages between two groups. Statistical significance was set at P less than 0.05. The regimen was planned for both chemotherapy-naive and chemotherapy-exposed patients. Thus, this trial was designed to detect a RR of 20% as compared with a minimal, clinically meaningful RR of 5%. A 'minimax' design was used for this study with 80% power to accept the hypothesis and 5% significance to reject the hypothesis. The total sample size was set to 27 patients.

Results

Patients' characteristics

A total of 28 patients were enrolled between May 2004 and July 2007, all of whom were evaluable for response and toxicity. Patients' baseline characteristics are shown in Table 1. Median age was 62 years (range: 37–73 years),

Table 1 Baseline patient and disease characteristics ($n=28$ patients)

Characteristic	No. of patients (%)
Median age, years (range)	62 (37–73)
Sex	
Male	13 (46)
Female	15 (54)
ECOG performance status	
0	3 (10)
1	15 (54)
2	10 (36)
Primary tumor site	
Intrahepatic bile duct	11 (39)
Extrahepatic bile duct	9 (32)
Gallbladder	6 (22)
Ampulla	2 (7)
Prior treatment	
Surgery	14 (50)
Radiotherapy	5 (18)
1st line chemotherapy	11 (39)
Fluoropyrimidines	5
Gemcitabine	5
Others	5
Disease state	
Recurrent	14 (50)
Metastatic	14 (50)
Location of metastatic site	
Lymph nodes	12 (43)
Liver	8 (28)
Peritoneum	4 (14)
Lung	3 (11)
Bone	2 (7)

ECOG, Eastern Cooperative Oncology Group.

and 13 patients were male. Ten patients (36%) had an ECOG performance status of 2. Intrahepatic bile duct cancer accounted for 39% of 28 patients. Fourteen patients received surgical treatment for primary biliary tract cancer and recurrence was noted to them. Eleven patients (39%) documented progression after first-line chemotherapy before entry into this study. These patients received mostly fluoropyrimidines (fluorouracil, capecitabine) or gemcitabine-based chemotherapy as first-line treatment. The disease control rate (DCR) of first-line chemotherapy was 54.5%, including one case of partial response (PR). The median time interval from first-line chemotherapy to entry into this study was 3.6 months [95% confidence interval (CI): 1.8–5.3]. Common metastatic sites were the lymph nodes (43%) and liver (28%).

Treatment and dose intensity

In total, 166 cycles of treatment were performed with a median of five cycles (range: 2–12 cycles) per patient. Fourteen patients (50%) received more than six cycles of treatment and six patients (21%) received more than nine cycles. The median relative dose intensity was 87% (29 mg/m^2/week) for oxaliplatin, and 99% (659 mg/m^2/week) for 5-FU. Dose reduction was carried out in three patients (10%). The causes of dose reduction were nausea and neutropenia. Fifteen cycles (9%) were delayed (median 2 weeks), most of which were related to general weakness. Sixteen patients (57%) switched over to the next chemotherapy regimen after disease progression was documented. The next chemotherapy regimen included oral 5-FU agent or gemcitabine-based regimens.

Efficacy

All patients were evaluable for efficacy. One patient achieved a complete response and five (17.9%) patients achieved a PR. The overall RR was 21.5% (95% CI: 6.2–36.7). Nine (32.1%) patients showed stable disease and the DCR was 53.6% (95% CI: 35.1–72.0). The median TTP and OS were 3.5 months (95% CI: 2.7–4.3) and 10.0 months (95% CI: 7.2–12.8), respectively (Figs 1 and 2). The 6-month and 12-month survival rates were 60.7 and 17.8%, respectively. No difference in efficacy was observed between the first-line and second-line treatment groups.

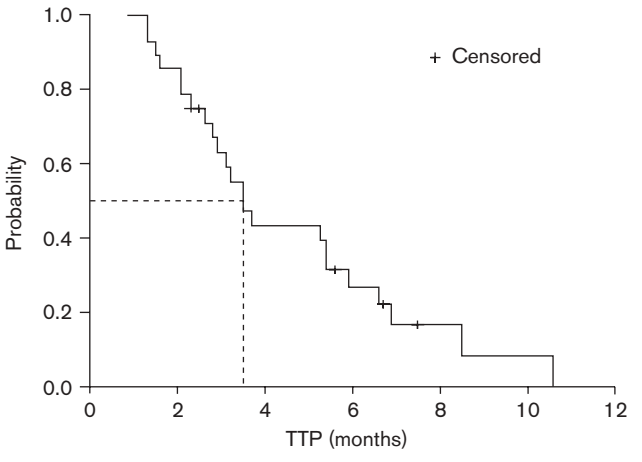
Safety

All patients were evaluable for toxicity (Table 2). No treatment-related death was observed. Grade 3 neutropenia was seen in five patients (18%). No grade 4 neutropenia and neutropenic fever were observed. Six patients (21%) were given G-CSF (mean 4.5 times per patient). Grade 3/4 anemia was observed in four patients (15%), and thrombocytopenia was observed in one patient (4%). Other grade 3/4 adverse events included two cases of nausea/vomiting and one case of sensory neuropathy. Furthermore, four patients (14%) developed grade 3 infection. Causes of infection were from biliary obstruction because of disease progression (two patients) and from an indwelling venous catheter (two patients).

Discussion

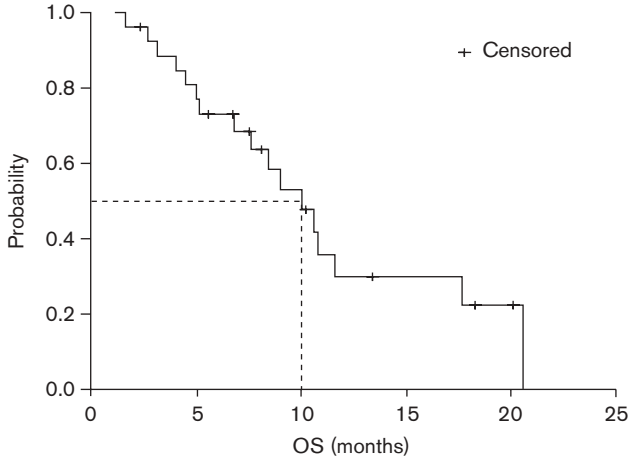
No standard regimen was established for the palliative treatment of biliary tract carcinoma patients. Eckel and

Fig. 1



Time to progression (TTP).

Fig. 2



Overall survival (OS).

Table 2 Grades 2–4 toxicities per patient ($n=28$)

	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	5 (18)	5 (18)	–
Lymphopenia	8 (28)	5 (18)	2 (7)
Thrombocytopenia	3 (11)	1 (4)	–
Anemia	6 (21)	3 (11)	1 (4)
Nausea/vomiting	11 (39)	2 (7)	–
Diarrhea	3 (11)	–	–
Peripheral neuropathy	1 (4)	1 (4)	–
Fatigue	2 (7)	1 (4)	–
Infection	–	4 (14)	–

Schmid [11] reported a pooled analysis in advanced biliary tract carcinoma in which publications of chemotherapy from 1985 to 2006 were included. In their report, pooled RR and DCR of palliative chemotherapy were 22.6 and 57.3%, respectively. The overall median TTP and OS were 4.1 and 8.2 months, respectively. They reported that gemcitabine and platinum-containing regimens demonstrated relatively high RR. In contrast, taxanes, irinotecan, or 5-FU monotherapy as well as targeted agents manifested relatively low efficacy. They concluded that based on published results of predominant phase II trials, gemcitabine and platinum compounds could be a reasonable choice for chemotherapy in advanced biliary tract cancer patients. A GERCOR (French Oncology Research Group) study [22] which evaluated activity and tolerability of gemcitabine combined with oxaliplatin showed relatively high RRs of 22–36%, and median progression-free survival of 3.9–5.7 months and median OS of 7.6–15.4 months.

Nehls *et al.* [20] evaluated the combination regimen of oxaliplatin, leucovorin, and 5-FU in patients with advanced biliary system cancer. Sixteen patients received oxaliplatin of 85 mg/m^2 per 2 h on day 1 concurrent with leucovorin 500 mg/m^2 per 2 h, followed by continuous 5-FU infusion of 1.5–2.0 mg/m^2 per 22 h on days 1 and 2. Their regimen was different to ours in doses and schedule. They achieved three PRs (19%) and six stable diseases (37.5%). The median TTP and OS were 4.1 and 9.5 months, respectively. Our study shows a RR of 21.5% and a DCR of 53.6% with a median TTP of 3.5 months (95% CI: 2.7–4.3) and a median OS of 10.0 months (95% CI: 7.2–12.8). Although the dose intensity of our study was lower than that of Nehls' study, the efficacy was comparable with their results.

In our study, both sex and age did not impact on DCR and survival. Although the DCR of patients with gallbladder cancer was higher compared with intrahepatic and extrahepatic bile duct cancer ($P = 0.015$), OS of both the groups did not show statistically significant difference ($P = 0.417$). The pooled analysis by Eckel and Schmid [11] demonstrated that gallbladder cancer showed better RR but shorter survival duration than cholangiocarcinoma. Owing to the small sample size of our study, our survival results seem to be different from those of pooled analysis.

No case of grade 4 neutropenia that required hospitalization was observed. Cases of sepsis were, however, documented in four patients and were related to biliary obstruction or implanted devices rather than drug-related neutropenia itself. Grade 2/3 nausea and vomiting happened relatively frequently (46%) but were manageable. Incidence of grade 2/3 neuropathy was trivial. Owing to the favorable toxicity profiles of this regimen, the patients who had an ECOG performance status of 2 and failed with first-line chemotherapy could receive chemotherapy without difficulty.

In our study, DCR and OS did not demonstrate a difference between the two patients groups who received oxaliplatin combined with leucovorin and 5-FU as first-line treatment and second-line treatment. This result must be interpreted in a limited scope because of the small number of the patients. Our results, however, suggest that this oxaliplatin-based chemotherapy has a lack of cross-resistance with gemcitabine or fluoropyrimidine-based first-line chemotherapy. Therefore, this regimen could be a reasonable choice as second-line chemotherapy for those who have failed with gemcitabine or fluoropyrimidine-based treatment. Studies with larger subject pools are necessary to further investigate this matter.

In conclusion, our results indicate that the combination regimen of oxaliplatin, leucovorin, and 5-FU is a feasible treatment alternative with a favorable safety profile in patients with recurrent/metastatic biliary tract cancer.

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