Original Article

Outcomes of FOLFOX4 Chemotherapy as a Second-Line Treatment for Advanced Biliary Tract Cancer

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Objective: After progression on platinum-gemcitabine, patients with advanced biliary tract cancer (aBTC) have limited treatment options. The objective of the present study was to evaluate the outcomes and adverse events of FOLFOX4 as a second-line chemotherapy.

Materials and Methods: This was a retrospective study included aBTC patients who previously treated with platinum/gemcitabine and received the FOLFOX4 regimen as a second-line treatment in Srinagarind Hospital between June 2014 and June 2018. Survival analysis was done using the Kaplan-Meier method and the log-rank test.

Results: A total of 19 patients of biliary tract cancer were included, the median age was 59 years (42 to 75), and 14 patients (73.6%) were male. Most patients had ECOG 1 and were intrahepatic subtype in primary. Two patients achieved partial response and 8 patients had stable disease. The median progression-free survival and overall survival (OS) were 2.6 and 6.2 months respectively. The 6- and 12-month survival rate was 52.6% and 11.8%. The median OS in patients who achieved disease control was significantly longer than who progressed on FOLFOX (9.1 vs. 4.7 months), hazard ratio 0.11 (95% CI 0.12 to 0.73, p=0.02). Grade 3 or higher adverse events were observed in seven patients (36.8%), with no patient discontinue the treatment from toxicity.

Conclusion: In patients with aBTC who progressed after platinum-gemcitabine, FOLFOX4 is effective with manageable toxicity.

Keywords: Advanced biliary tract cancer; Second-line chemotherapy; FOLFOX; Cholangiocarcinoma

J Med Assoc Thai 2021;104(Suppl.4): S14-8
Website: http://www.jmatonline.com

Biliary tract cancer (BTC) arises from epithelial cells of the bile ducts. The Northeastern part of Thailand has the highest prevalence globally. Most patients seeking medical attention already have the locally advanced or metastatic disease[1].

The standard treatment of BTC is surgery in early-stage and palliative chemotherapy in advanced stage[2]. In 2010, the ABC-02 phase III study demonstrated that cisplatin plus gemcitabine was associated with a significant survival advantage without the addition of substantial toxicity in locally advanced or metastatic BTC. However, the median overall survival in this trial was only 11.7 months and the median progression-free survival was 8.0 months[3].

Although there is no established treatment after progression from first-line chemotherapy, fluoropyrimidine-based regimens are commonly used. FOLFOX4 regimen was studied in a phase II study including 37 advanced BTC patients who progressed on cisplatin-gemcitabine. The results showed the median overall survival of 6.9 months and the median time to progression of 3.1 months[4].

The ABC-06 trial, a randomized phase III study comparing active symptom control (ASC) with mFOLFOX versus ASC alone. In the treatment arm, the median overall survival was 6.2 months, and the 6- and 12-month survival rates were 50.6% and 25.9%, respectively. When compared to the ASC clone, FOLFOX4 regimen improved survival with the hazard ratio (HR) of 0.69[5].

However, there is still limited data regarding the benefit and the safety of second-line chemotherapy in advanced BTC. In this study, we aimed to explore the survival benefit and safety of FOLFOX4 after progression on cisplatin and gemcitabine.

Materials and Methods

Study design

This was a retrospective study that included advanced biliary tract cancer patients who received FOLFOX4 as second-line chemotherapy in Srinagarind Hospital, Khon Kaen, Thailand from June 2014 to June 2018. Clinical records (age, weight, height, sex, and performance status), radiographic and pathological, and laboratory data were retrospectively reviewed.

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How to cite this article:

Sookprasert A, Cheewasathianchai P, Wirasorn K, Sanlung T, Watcharenwong P, Chindaprasirt J. Outcomes of FOLFOX4 Chemotherapy as a Second-Line Treatment for Advanced Biliary Tract Cancer. J Med Assoc Thai 2021;104 (Suppl5): S14-8.

doi.org/10.35755/jmedassocthai.2021.S04.00039

The study was approved by the Khon Kaen University Ethics Committee for Human Research based on the Declaration of Helsinki (Number HE631254).

Patients

Patients were included if they were 18 years of age or older; had a diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, ampullary or gallbladder cancer); progressed after combination chemotherapy of platinum (cisplatin or carboplatin) and gemcitabine as first-line treatment; received at least one cycle of FOLFOX4 regimen as second-line treatment. Patients were excluded if they had other active cancers or no clinical evaluation after chemotherapy.

Treatment

All patients received FOLFOX4 regimen for up to 24 weeks. It comprised of Leucovorin (200 mg/m^2), Oxaliplatin (85 mg/m^2), 5FU (400 mg/m^2), 5FU (600 mg/m^2) on day 1 and Leucovorin (200 mg/m^2), 5FU (400 mg/m^2), 5FU (600 mg/m^2) on day 2 as shown in Figure 1.

Definition

Progression-free survival was defined as the time from the first day of FOLFOX and radiological disease progression or clinical progression or death of any cause, whichever occurred first). Overall survival was calculated from the date of FOLFOX until the date of death from any cause. Tumor response was evaluated using RECIST 1.1 criteria[6] and adverse events grading was done according to CTCAE version 4.0.

Statistical analyses

Demographic data were analyzed using descriptive statistics. Safety analysis was performed on all the patients. The overall response rate was assessed in the response-evaluable patients, defined as patients who had measurable disease at baseline, and had one or more post-baseline scans or experienced disease progression. Overall survival was analyzed using the Kaplan-Meier curves and the log-rank test. A Cox proportional-hazards model was used to estimate the hazard ratios. A p-value of <0.05 was statistically significant in all tests. All data analyses were carried out using STATA software (StataCorp LP, College Station, TX, USA).

Results

From June 2014 through June 2018, a total of 192 patients received gemcitabine-based chemotherapy for biliary tract cancer, and 27 patients received FOLFOX as a second-line treatment. Eight patients were excluded due to incomplete medical records, and 19 patients were included in the present study.

The median age was 59 years (range 42 to 75) and most of the patients were male (73.6%). As shown in Table 1, only 3 patients had an ECOG performance status of 0 and 15 patients (78.6%) had intrahepatic cholangiocarcinoma as a primary site. All patients had metastatic

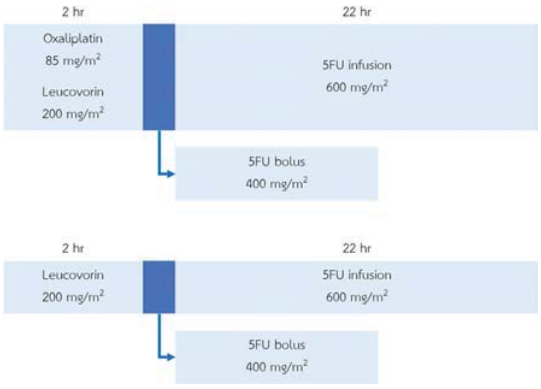

Figure 1. FOLFOX4 regimen.

Table 1. Baseline characteristics

Characteristics	n=19	Percent
Age (years), median	59.7 (42 to 75)	
Sex		
Male	14	73.6
Female	5	26.3
Body weight (kg), median	56.9 (42.8 to 72.5)	
Height (cm), median	158.9 (145 to 170)	
ECOG performance		
0	3	15.8
1	16	84.2
Underlying disease		
Diabetes mellitus	4	21.1
Hypertension	5	26.3
Liver disease	1	5.3
Chronic renal disease	1	5.3
Other	1	5.3
Primary site		
Intrahepatic cholangiocarcinoma	15	78.9
Extrahepatic cholangiocarcinoma	2	10.5
Ampullary	2	10.5
Gall bladder	0	0
Metastatic sites		
Liver	10	52.6
Lung	11	57.9
Peritoneum	4	21.1
Bone	2	10.5
Lymph nodes	3	15.8
CA19-9 (U/mL), median	342.8 (1.04 to 1,000)	

disease with the most common sites were lungs (57.9%) and liver (52.6%). The median CA19-9 before treatment was 342.8 U/mL.

Treatments

The prior treatments received are shown in Table 2. Seven patients (36.8%) initially underwent curative surgery and 4 patients (21.1%) had palliative biliary drainage. The median number of platinum/gemcitabine was 6 and 9 patients (47%) achieved tumor response. Six patients were classified as platinum-sensitive.

The median time from the last dose of platinum/gemcitabine to FOLFOX was 97 days (range 14 to 455). The median number of cycles of FOLFOX was 4 with only 6 patients (31.5%) received more than 6 cycles.

The most common reason to stop the chemotherapy was clinical and radiological progression (47.4% and 26.3%, respectively). No patients discontinued the treatment due to the reason for unacceptable toxicity and four patients completed the treatment protocol.

Table 2. Prior treatments

Characteristics	n=19	Percent
Curative surgery	7	36.8
Biliary drainage	4	21.1
CA19-9 before FOLFOX (U/mL) (n=16), median	342.8 (1.04 to 1,000)	
1st line chemotherapy		
Cisplatin/Gemcitabine	15	79
Carboplatin/Gemcitabine	4	21
Number of platinum/gemcitabine (cycle), median	6 (4 to 8)	
Best response of first-line		
Progressive disease	2	10.5
Stable disease	8	42.1
Partial response	9	47.4
Complete response	0	0
Platinum sensitive	6	31.6
Platinum refractory	13	68.4

Table 3. The response rate of FOLFOX (n=18)

Results	n	Percent
Best response		
Complete response (CR)	0	0
Partial response (PR)	2	11.1
Stable disease (SD)	8	44.4
Progressive disease	8	44.4
Objective response rate (ORR)	2	11.1
CBR (CR+PR+SD)	10	55.5

Tumor response and survival

The objective tumor response was evaluable in 13 patients (5 patients had clinical progression or 1 patient was lost to follow-up). No patient achieved a complete response, and the objective response rate was 11.1%. Tumor control (complete or partial response or stable disease) was achieved in 10 of 18 patients (55.5%).

Figure 2A shows the Kaplan-Meier curves for the overall survival of the entire cohort. The median overall survival was 6.2 months (95% CI 2.9 to 9.5). The 6- and 12-month survival rate was 52.6% and 11.8% respectively. The median progression-free survival was 2.6 months (95% CI 1.6 to 7.4) as shown in Figure 2B. The median survival in patients who achieved tumor control (PR+SD) was 9.1 months, as compared with 2.95 months for those with progressive disease. It was significantly longer with the hazard ration of 0.20 (95% CI 0.06 to 0.62) as shown in Figure 3. The median survival in the platinum-sensitive group was slightly longer than the platinum-refractory group (6.2 vs. 5.1 months) with the HR of 0.58 (95% CI 0.16 to 2.05).

Toxicities

Total adverse events are summarized in Table 4. The most common adverse events were hematologic toxicities; anemia in 16 patients (84.2%), decreased platelet in 9 patients (47.4%), and neutropenia in 6 patients (3.6%). No febrile neutropenia was observed. Adverse events of grade 3 or higher were found in 7 patients (36.8%); AST elevation and increased total bilirubin. No toxicity-related death was observed.

Discussion

In the present study in patients with advanced BTC previously treated with platinum-gemcitabine, FOLFOX4 was effective and safe and resulted in an ORR of 11% in a real-world setting. The observed PFS and OS were 2.6 and 6.2 months.

In the current study, the FOLFOX regimen was slightly different from the original ABC-06 study, a phase 3 trial randomized patients to second-line modified FOLFOX versus active symptom control. The regimen in the current study used lower folinic acid and fluorouracil doses and had a shorter fluorouracil infusion time. Moreover, not all patients in the study received the standard ABC-02 gemcitabine/cisplatin regimen in the first-line setting as in the ABC-06 protocol. Some patients were cisplatin-ineligible and had received carboplatin instead. These two factors could demise the outcome of treatment. Despite the difference, the survival of FOLFOX in our study was consistent with those in the ABC-06 trial of 6.2 months.

The overall survival in this study was comparable to several retrospective studies in aBTC patients treated with systemic chemotherapy in the second-line setting[7,8]. The median OS reported ranged from 6.2 months to 7.5 months. In the systematic review by Lamarca et al, the overall survival was 7.2 months[9]. Recently a phase 2 study of FOLFIRINOX as a second-line treatment revealed the OS

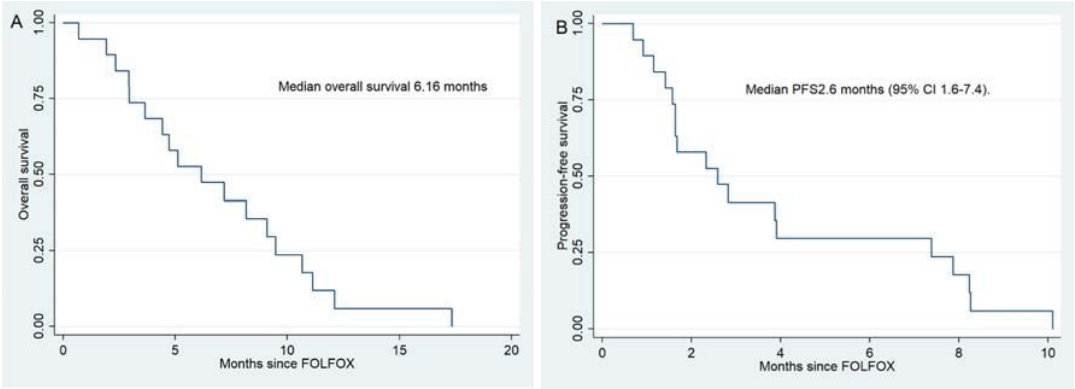

Figure 2. Survival in patients with advanced biliary tract cancer who received FOLFOX regimen as second-line therapy. A) overall survival, and B) progression-free survival.

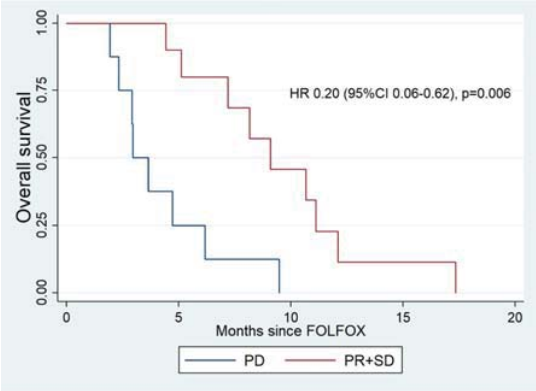

Figure 3. Overall survival comparing patients who achieved tumor control (PR+SD) and patients who had progressive disease.

Table 4. Adverse events during the treatment of FOLFOX

	Grade 1 to 2 n (%)	Grade 3 to 4 n (%)
Anemia	16 (84.2)	0
Neutropenia	6 (31.6)	0
Platelet decreased	8 (42.1)	1 (5.3)
Febrile neutropenia	-	0
AST increased	8 (42.1)	2 (10.5)
ALT increased	9 (47.4)	1 (5.3)
Total bilirubin increased	4 (21.1)	2 (10.5)
Biliary tract infection	0	1 (5.3)
Creatinine increased	4 (21.1)	0
Peripheral neuropathy	0	0
Nausea	2 (10.5)	0
Vomiting	0	0
Oral mucositis	0	0
Diarrhea	0	0
Anorexia	4 (21.1)	0
Fatigue	5 (26.3)	0

of 10.7 months with tolerable toxicity[10,11].

The OS in those who did not progress was significantly longer than progressive disease group. However, there was no trend towards better OS in the platinum-sensitive group, unlike the ABC-06 results.

Systemic treatment for biliary tract cancer has become personalized according to the mutational target such as FGFR, IDH-1, and BRAF mutation[12-15]. However, the mutational target in BTC is not common and most of the actionable targets found were studied in the US or Europe in which different carcinogenesis from Asian patients. The distinct etiology and different genomic and epigenomic alterations led to the variation of molecular subtypes among the patients[16]. As a result, implementing targeted treatment is still a challenge and chemotherapy is still a good option for good performance status patients regardless of mutational property. Predictive markers for benefit of chemotherapy are warranted to highly select patients who would benefit from the treatment.

FOLFOX was well tolerated in the second-line setting in BTC. The most common grade 3 to 4 hematologic adverse event was thrombocytopenia. However, the events were less frequently observed because of the retrospective nature of the study.

The main limitation of this study was the small sample size. Because the use of FOLFOX as a second-line

treatment was introduced not long ago and it was not on the national drug list for CCA yet, only a few patients did receive the drugs.

In conclusion, this study shows the benefit of FOLFOX as a second-line treatment in patients with BTC with acceptable toxicity profiles. FOLFOX is an option for patients who progressed on platinum-gemcitabine. Further studies addressing the quality of life and cost-effectiveness are warranted as they both are very important issues[17].

What is already known on this topic?

Advanced biliary tract cancer is the aggressive tumor with low response to chemotherapy. Only one randomized controlled trial reported the overall survival benefit of second line chemotherapy when compared with active symptom control. Currently, there is limited real-word data of such patients.

What this study adds?

In the present study, the authors report the real-life evidence of the effectiveness and toxicity of the second-line chemotherapy in biliary tract cancer.

Acknowledgements

We thank the Department of Medicine, Faculty of Medicine, Khon Kaen University for the publication support.

Potential conflicts of interest

The authors declare no conflict of interest.

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