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ORIGINAL ARTICLE

Second-Line Chemotherapy in Advanced Biliary Tract Cancer: A Retrospective Analysis

Hyun Jung Kim[1], Jina Yun[1], Han Jo Kim[2], Kyoung Ha Kim[3], Se Hyung Kim[1], Sang-Cheol Lee[2], Sang Byung Bae[2], Chan Kyu Kim[1], Nam Su Lee[3], Kyu Taek Lee[2], Seong Kyu Park[1], Jong-Ho Won[3], Hyun Jong Choi[4], Jong Ho Moon[4], Dae Sik Hong[1]

[1]Division of Hematology & Oncology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon; [2]Division of Hematology & Oncology, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan; [3]Division of Hematology & Oncology, Department of Internal Medicine, Soonchunhyang University Seoul Hospital, Seoul; [4]Division of Gastroenterology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea

Objective: The evidence of 2nd line chemotherapy has not been validated. We investigated the treatment outcomes of 2nd line palliative chemotherapy in patients with biliary tract cancer (BTC) and analyzed the factors affecting response or survival.
Methods: We retrospectively reviewed and analyzed the outcomes in advanced BTC patients who underwent 2nd line chemotherapy in Soonchunhyang Universitiy Hospitals (Bucheon, Seoul, and Cheonan).
Results: From December 2004 to May 2014, 65 patients were enrolled. The median age was 56 years (range, 40 to 76 years) and the ratio of cholangiocarcinoma (intrahepatic or extrahepatic), gall bladder cancer, and ampulla of Vater cancer was 41 (63.1%):18 (27.7%):6 (9.25%). Half of the patients (33 patients, 50.8%) were treated with gemcitabine-based and 28 patients (43.1%) with 5-fluorouracil-based therapy. The response rate was 3.0% and disease control rate was 21.5% in intention-to-treat analysis. Median overall survival (OS) was 7.2 months (95% confidence interval [CI], 3.9 to 10.5 months) and median progression free survival (PFS) was 3.7 months (95% CI, 2.5 to 4.9 months). In multivariate analysis, patients with good performance status (PS) (P = 0.001) and chemo-sensitive tumor to 2nd line chemotherapy (P = 0.000) had longer PFS as compared to the others. In addition, patients with good PS (P = 0.003), chemo-sensitive tumor to 1st line (P = 0.046), and 2nd line chemotherapy (P = 0.004) were good prognostic factors for OS.
Conclusion: The effect of 2nd line chemotherapy in advanced BTC was modest and maybe beneficial in select patients.

Keywords: Biliary tract neoplasms; Drug therapy; Salvage therapy

INTRODUCTION

Biliary tract cancer (BTC) is generally rare in Western countries but common in Korea where approximately 5,130 new patients were diagnosed in 2012 [1]. Treatment of BTC is limited, and although surgery provides the only curative treatment, most patients are not eligible for surgery because of advanced stage at diagnosis or combined impaired liver function. Therefore, there is a need for palliative chemotherapy for inoperable BTC patients. Previous study demonstrated an improvement of overall survival (OS) and quality of life for patients receiving chemotherapy versus best supportive care [2,3]. In addition, gemcitabine–cisplatin combination was identified as the new standard 1st-line therapy in advanced BTC [4] as compared to gemcitabine monotherapy. In this phase III study, the median progression free survival (PFS) was 8.5 months as compared to the approximately 4–6 months in other phase II studies [5-7]. At the time of failure to 1st line therapy, some patients who were able to maintain good performance status (PS) went into salvage therapy. There is a need to develop salvage chemotherapy to improve the outcome of advanced BTC. However, 2nd line therapy has not validated as compared to the many efforts to improve front line therapy in BTC patients. Randomized trial is difficult due to the rarity of the tumor with progression to 1st line therapy. Therefore, we investigated the treatment outcomes such as the effect and toxicities of 2nd line palliative chemotherapy in BTC patients and evaluated factors affecting response or survival.

Correspondence to: Chan Kyu Kim
Division of Hematology & Oncology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, 170 Jomaru-ro, Wonmi-gu, Bucheon 14584, Korea
Tel: +82-32-621-5186, Fax: +82-32-621-5018, E-mail: md53097@schmc.ac.kr
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MATERIALS AND METHODS

1. Patients and methods

1) Patient eligibility

From December 2004 to May 2014, the patients with histologic confirmed adenocarcinoma locally advanced or metastatic BTC patients (including extrahepatic cholangiocarcinoma, intrahepatic cholangiocarcinoma [IHCC], gallbladder cancer [GB ca], and ampulla of Vater cancer), who underwent 2nd line chemotherapy in Soonchunhyang University Hospitals (Bucheon, Seoul, and Cheonan), were retrospective reviewed through medical records. Patients who were previously treated with radiotherapy or concurrent chemoradiotherapy were eligible if treated with other systemic 1st line palliative chemotherapy. This study was approved by the institutional review board of Soonchunhyang University Hospitals (2014-11-007-002).

2) Response and toxicity assessment

Tumor response measured by the RECIST ver. 1.0 (Response Evaluation Criteria in Solid Tumors) was evaluated with the same imaging modality used at baseline, including contrast enhanced computed tomography or magnetic resonance imaging. Hematologic and non-hematologic toxicities were evaluated using the NCI-CTCAE ver. 3.0 (National Cancer Institute Common Terminology Criteria for Adverse Events; National Cancer Center, Goyang, Korea). All patients were included in the intention-to-treat (ITT) analysis of efficacy. The response rate was calculated as the ratio of the number of patients who achieved complete or partial responses to the number of patients enrolled in the study. The disease control rate (DCR) was calculated as the ratio of the number of patients who achieved complete or partial responses or stable disease (SD) to the number of patients enrolled in the study.

2. Statistical analysis

Factors that influence treatment response were analyzed through chi-square or Fisher's exact test. PFS was calculated from the first day of 2nd line treatment to the date on which progression of the disease was first observed or the date of last follow-up. OS was defined from the first date of 2nd line treatment to the date of death or last follow-up. OS and PFS were assessed using the Kaplan-Meier method, and the 95% confidence intervals (95% CIs) for the median time to an event were calculated. Significant variables in the univariate analysis were considered as variables for the multivariate analysis performed using Cox's proportional hazard regression model. The SPSS ver. 14.0 statistical software program (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

1. Patient characteristics

From December 2004 to May 2014, 65 patients were enrolled in the retrospective study. The baseline characteristics of patients were summarized in Table 1. The median patient age was 56 years (range, 40 to 76 years). The male to female ratio was 34:31. Approximately half of the patients had IHCC as primary site and 18 patients had GB ca. Only 1 patient (1.5%) had an European Cooperative Oncology Group (ECOG) PS of 0; 41 (63.1%), 21 (32.3%), and 2 (3.15) patients had ECOG PS of 1, 2, and 3, respectively. Twelve patients (18.5%) had locally advanced BTC and 53 patients (81.5%) had recurrent or metastatic disease. Previous palliative chemotherapy mainly consisted of 5-fluorouracil (5FU)-based (5FU/cisplatin, 5FU/leucovorin, 5FU/leucovorin/oxaliplatin, capecitabine alone; n=38; 58.5%) and gemcitabine-based therapy (gemcitabine alone, gemcitabine/cisplatin, gemcitabine/oxaliplatin; n=24; 36.9%). Thirty-seven patients (56.9%) were primarily refractory to 1st line palliative chemotherapy, while 15 patients (23.1%) and 13 patients (20.0%) were partial responses and SD to previous chemotherapy, respectively. Only 8 patients had disease progression during the chemotherapy-off period to previous palliative chemotherapy and other patients had disease progression during prior chemotherapy. Baseline median albumin level and estimated glomerular filtration rate (eGFR) before 2nd line chemotherapy were 3.8 g/dL (range, 2.5 to 4.8 g/dL) and 89 mL/min (range, 32.2 to 149.5 mL/min), respectively.

2. Treatment efficacy and toxicities of 2nd line chemotherapy

Among 65 patients, most had undertaken gemcitabine-based (gemcitabine alone, gemcitabine/cisplatin, gemcitabine/oxaliplatin; n=33; 50.8%) and 5FU-based chemotherapy (5FU/cisplatin, 5FU/leucovorin, 5FU/leucovorin/oxaliplatin, oral 5FU alone; n=29; 44.6%). Few others (n=3, 4.6%) were treated with anthracyline or bevacizumab combination. Response evaluation was done in 54 patients. Two of 65 patients had a PR to 2nd line chemotherapy and 12 patients (18.5%) had SD. In ITT analysis, overall response rate (ORR) and DCR were calculated as 3.0% and 21.5%, respectively (Table 2). Median overall OS was 7.2 months (95% CI,

3.9 to 10.5 months) and median PFS was 3.7 months (95% CI, 2.5 to 4.9 months) (Fig. 1).

Treatment related toxicities were assessable in all patients (Table 3). Adverse events during treatment were predominately grade (Gr) 1-2, except for neutropenia. Among hematologic toxicities, Gr 3-4 neutropenia was detected in 24 patients (36.9%), but only 3 patients experienced neutropenic fever. Gr 3-4 anemia and thrombocytopenia were developed in 9 patients (13.85) and 13 patients (20.0%), respectively. Most of non-hematologic toxicities were Gr 1-2. Severe Gr 3-4 non-hematologic toxicities were anorexia, fatigue, emesis, stomatitis, and diarrhea in 5 cases (7.7%), 4 cases (6.2%), 2 cases (3.1%), and 2 cases (3.1%), respectively.

Table 1. Baseline characteristics of patients with advanced BTC (N=65)

Characteristic	Value
Men	34 (52.3)
Median age (range) (yr)	56 (40-76)
Primary tumor site	
Extrahepatic BTC	7 (10.8)
Intrahepatic BTC	34 (52.3)
Gallbladder cancer	18 (27.7)
Ampulla of Vater cancer	6 (9.2)
ECOG PS[a]	
0-1	42 (64.6)
2-3	23 (35.4)
Disease pattern	
Locally advanced	12 (18.5)
Recurrent or metastatic	53 (81.5)
Previous chemotherapy	
5-Fluorouracil-based	38 (58.5)
Gemcitabine-based	24 (36.9)
Others	3 (4.6)
Best response to previous chemotherapy	
Partial response	15 (23.1)
Stable disease	13 (20.0)
Progressive disease	37 (56.9)
Median albumin (range) (g/dL)	3.8 (2.5-4.8)
Median estimated glomerular filtration rate (range)	89 (32.2-149.5)

Values are presented as number (%), unless otherwise stated.
BTC, biliary tract cancer.
[a]European Cooperative Oncology Group performance status.

3. Prognostic factors

Among the types of 2nd line therapy, sex, age, primary tumor site, disease pattern, carbohydrate antigen 19-9 value, efficacy to the 1st line therapy, ECOG PS, albumin level, and eGFR, none was a significant factor on the effect of the 2nd line therapy (Table 4).

Table 2. The kinds of 2nd line therapy and response to 2nd line therapy (N=65)

Variable	Value
The kinds of 2nd line chemotherapy	
5-Fluorouracil-based	28 (43.1)
Gemcitabine-based	33 (50.8)
Others	4 (6.2)
Response to 2nd line therapy	
Complete response	0
Partial response	2 (3.1)
Stable disease	12 (18.5)
Progressive disease	40 (61.5)
Not assessed	11 (16.9)
Response rate by ITT analysis (%)	3.0
Disease control rate by ITT analysis (%)	21.5

Values are presented as number (%), unless otherwise stated.
ITT, intention to treat.

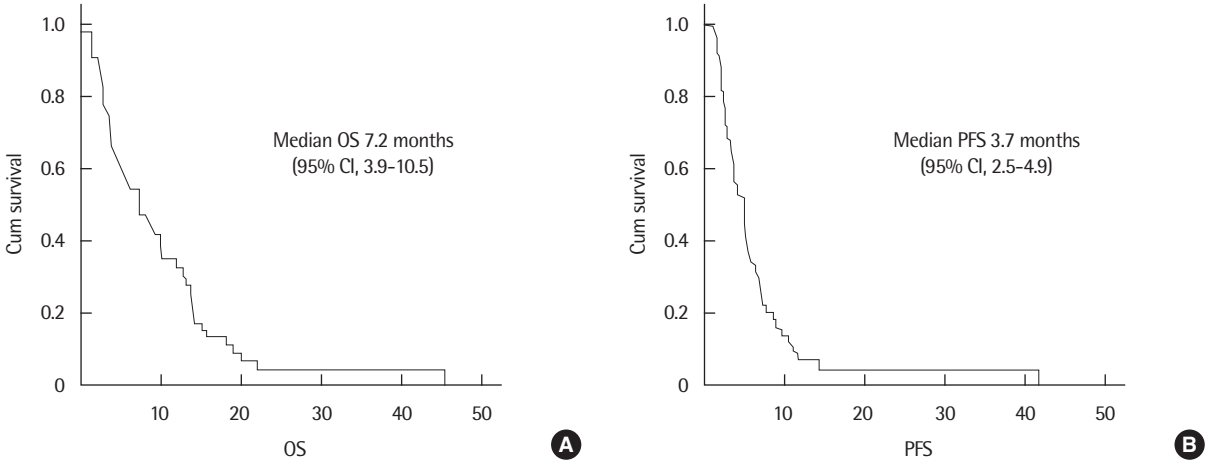

Fig. 1. Kaplan-Meier curves for (A) the overall survival and (B) progression free survival in patients with advanced biliary tract cancer who underwent 2nd line chemotherapy. OS, overall survival; PFS, progression free survival; CI, confidence interval.

Table 3. Treatment–related toxicities

Toxicities	Grade 1-2	Grade 3-4
Hematologic toxicities		
Neutropenia	18 (27.7)	24 (36.9)
Neutropenia fever	-	3 (4.6)
Anemia	35 (53.9)	9 (13.8)
Thrombocytopenia	30 (46.2)	13 (20.0)
Non-hematologic toxicites		
Anorexia	40 (63.0)	5 (7.7)
Fatigue	22 (33.8)	4 (6.2)
Emesis	37 (56.9)	2 (3.1)
Stomatitis	22 (33.9)	2 (3.1)
Diarrhea	2 (3.0)	1 (1.5)
Peripheral neuropathy	13 (20.0)	0

Values are presented as number (%).

Table 4. Factors that influence treatment response to 2nd line therapy

Factors	P-value[a]
Kinds of 2nd line therapy	0.562
Sex (male vs. female)	0.546
Age (≥ 56 yr vs. < 56 yr)	0.371
Primary tumor site	0.763
Disease pattern	0.164
Carbohydrate antigen 19-9 value (≥ 800 vs. < 800)	0.721
Efficacy to 1st line therapy	0.129
European Cooperative Oncology Group performance status (0 or 1 vs. 2 or 3)	0.464
Albumin level (≥ 3.8 vs. < 3.8)	0.06
Estimated glomerular filtration rate (> 89 vs. ≤ 89)	1.0

[a]This value was analyzed by cross-table analysis through SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA).

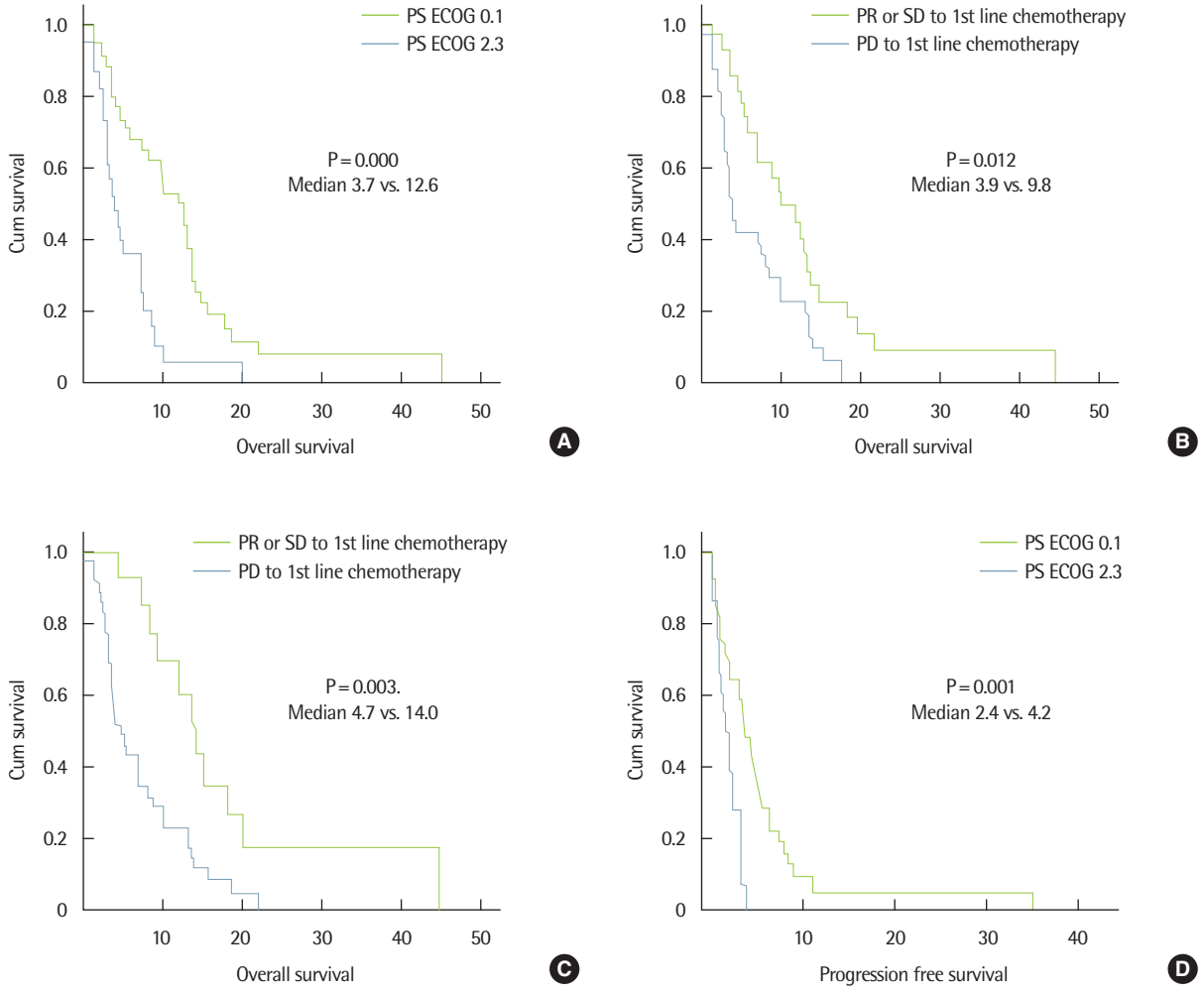

Fig. 2. Kaplan-Meier survival curves of the overall survival according to (A) ECOG PS, (B) efficacy to 1st line chemotherapy and (C) efficacy to 2nd line chemotherapy, and (D) Kaplan-Meier survival curves of the progression free survival according to ECOG PS. ECOG PS, European Cooperative Oncology Group performance status; PR, partial responses; SD, stable disease; PD, progressive disease.

Table 5. Prognosis factors for survival by univariate analysis

Factors	P-value[a]	
	Overall survival	Progression free survival
Kinds of 1st line therapy	0.232	0.268
Kinds of 2nd line therapy	0.856	0.144
Sex (male vs. female)	0.557	0.872
Age (≥56 yr vs. <56 yr)	0.942	0.376
Primary tumor site	0.111	0.719
Disease pattern	0.837	0.762
Carbohydrate antigen value (≥800 vs. <800)	0.370	0.434
European Cooperative Oncology Group performance status (0 or 1 vs. 2 or 3)	0.000	0.001
Efficacy to 1st line therapy	0.012	0.115
Efficacy to 2nd line therapy	0.003	0.000
Albumin (≥3.8 vs. <3.8)	0.085	0.070
Estimated glomerular filtration rate (>89 vs. ≤89)	0.582	0.895

[a]This value was analyzed by Kaplan-Meier method through SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA).

The patients with good PS, chemo-sensitive tumor to 1st line, or 2nd line chemotherapy were good prognostic factor of OS in univariate analysis (Fig. 2A-C). The ECOG PS and efficacy to 2nd line chemotherapy were also good prognostic factors to PFS in univariate analysis (Table 5, Fig. 2D).

In multivariate analysis, patients with good PS (P = 0.001) and chemo-sensitive tumor to 2nd line chemotherapy (P = 0.000) had longer PFS as compared to the others (Table 6). In addition, good PS status (P = 0.003), chemo-sensitive tumor to 1st line (P = 0.046), and 2nd line chemotherapy (P = 0.004) were good prognostic factors for OS (Table 6).

DISCUSSION

BTC is a highly lethal tumor and the prognosis of patients with advanced BTC is poor. The survival benefit of chemotherapy over best supportive care for advanced BTC was initially suggested in a phase III trial on advanced pancreatic and biliary tract cancers [2]. There have been many phase II studies for 1st line chemotherapy in patients with advanced BTC [5-7] and the results of a pooled analysis of 104 trials that included 2,810 patients with advanced BTC showed that response rates and tumor control were higher for the subgroup of patients receiving a combination of gemcitabine and platinum based agents [8]. In an advanced biliary cancer (ABC)-02 study, which enrolled 410 patients with advanced BTC,

Table 6. Prognosis factors for survival by multivariate analysis

Factors	P-value[a]	
	Overall survival	Progression free survival
European Cooperative Oncology Group performance status	0.003	0.001
Efficacy to 1st line therapy	0.046	-
Efficacy to 2nd line therapy	0.004	0.000

[a]This value was analyzed by Cox's proportional hazard regression model through SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA).

the combination of gemcitabine and cisplatin improved OS and PFS by 30% over gemcitabine alone [4]. Based on this phase III study, gemcitabine plus cisplatin combination chemotherapy has also become the accepted standard therapy in advanced BTC in Korea. While there have been several phase II studies and few phase III studies on 1st line therapy, there are few studies on salvage therapy in a patients with advanced BTC until now.

In case of advanced BTC, patients progressing after 1st line chemotherapy show rapidly worsening PS, and only a small number of patients sustain a general condition conducive to the administration of salvage treatment. Therefore, only a few clinical trials on salvage treatment of BTC have been conducted. Generally, experience of salvage therapy in advanced BTC has been sparse with disappointing results. There are very few active chemotherapy drugs besides gemcitaibine plus cisplatin combination therapy. Other cytotoxic drugs such as 5FU, adriamycin, oxalipatin, and mitomycin were used in phase II study in the salvage setting and other biologic agent included erlotinib, bevacizumab, cetuximab, or mTOR inhibitor.

In case of 5FU-based therapy in 1st line therapy, phase II study of salvage therapy with gemcitabine was reported by Oh et al. [9]. In the 29 patients, an ORR of 6.9%, median time to progression of 1.6 months, and median OS of 4.1 months was reported. In case of gemcitabine-based therapy in 1st line therapy, phase II study of salvage therapy was done with S-1 based [10,11], FAM (5FU, adriamycin and mitomycin) [12], or capecitabine based therapy [13]. Less than 10% of response rate was noticed and less than 7 months of OS was reported, with the exception of a report by Sasaki et al. [11]. The benefit of 2nd line chemotherapy in BTC as compared to best supportive care (BSC) has not yet been confirmed. In an ABC-02 study [4], 15.3% BTC patients were treated with 2nd line chemotherapy, while 75% total patients received 2nd line chemotherapy in the BT-22 study [14]. However, the median OS of the 2 large studies were similar at approximately 11 months (11.7 months vs.

11.2 months). Thus, BSC is the standard of care so far.

The ABC-06 trial is a phase III randomized trial to determine whether patients with advanced BTC benefit from the addition of mFOLFOX chemotherapy over active symptom control in the 2nd line setting, after progression of 1st line treatment with gemcitabine and cisplatin. It will be the first randomized phase III in the 2nd line setting. We expect that the benefit of 2nd line therapy in advanced biliary tract cancer could be demonstrated in this study.

In a recent review on 2nd line chemotherapy by Lamarca et al. [15] that included 25 studies of 761 patients, the mean OS was 7.2 months and PFS was 3.2 months, with RR 7.7% and DCR 49.5%. The result was similar to our study, but the RR or DCR in our report was inferior to the Lamarca's report. In our study, 11 patients were not evaluated for chemo-response, therefore, the factors of ITT analysis with retrospective study may result in an inferior response rate as compared to Lamarcar's results. In addition, ECOG PS 2-3 patients were 35.4% of the total patients in our study population and recurrent or metastatic disease were 81.5%. These unfavorable factors may have affected poor outcomes as compared to other studies. We found a modest effect of 2nd line chemotherapy based on literature review and our report.

We analyzed several factors by univariate and multivariate analysis to determine affecting and prognostic factors to chemo-response and survival. We identified no significant factors affecting the chemo-response in 2nd line chemotherapy.

In multivariate analysis, the patients with good PS status ($P = 0.001$) and chemo-sensitive tumor to 2nd line chemotherapy ($P = 0.000$) had longer PFS as compared to others. In addition, patients with good PS status ($P = 0.003$), chemo-sensitive tumor to 1st line ($P = 0.046$), and chemo-sensitive tumor to 2nd line chemotherapy ($P = 0.004$) were good prognostic factors for OS. Other prognostic factors such as albumin level reported by Oh et al. [9]' report or doublet regimen type recognized by Walter et al. [16] were not significant in the current study. Patients with good PS were confirmed as good prognostic factors to PFS or OS in our study as well as earlier studies.

Based on these results, we suggest that patients with poor PS should not be offered 2nd line chemotherapy. Patients with good PS and chemo-sensitive in 1st line may be considered as candidates for 2nd line chemotherapy.

Novel agents that target anti-angiogenic or eGFR/Her2/RAS/RAF pathway inhibitors have been tested mainly in 1st line, alone, or in combination with cytotoxic chemotherapy, however, the outcomes have been disappointing so far. Cetuximab was tested as combination regimen with gemcitabine and oxaliplatin in the 1st line setting, however the randomized phase II trial did not demonstrate the additional effect of cetuximab [17]. Some agents such as MEK inhibitor, selumetinib, or the combination of bevacizumab-erlotinib are possible effective drugs in 1st or 2nd line setting as reported on phase II study [18,19]. However, further investigation with novel targeting agent is needed for advanced BTC.

Our study was a retrospective study with a small number of patients. Therefore, there is limitation to the interpretation of the results. However, we found that outcomes of the 2nd line chemotherapy in patients with advanced BTC and prognostic factors. Our results indicated that prospective study on advanced biliary tract cancer with good PS and chemo-sensitive tumor for 2nd line chemotherapy is warranted.

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