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Natural history of metastatic biliary tract cancer (BTC) patients with good performance status (PS) who were treated with only best supportive care (BSC)

Jun Ho Ji[1,†], Haa-Na Song[2,†], Rock Bum Kim[3], Sung Yong Oh[4], Ho Yeong Lim[5], Joon Oh Park[5], Se Hoon Park[5], Moon Jin Kim[5], Soon Il Lee[6], Sung Hyeok Ryou[6], In Gyu Hwang[7], Joung-Soon Jang[7], Hong Jun Kim[8], Jun Young Choi[9], and Jung-Hun Kang[2,*]

[1]Division of Hematology and Oncology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, [2]Division of Hematology-Oncology, Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, [3]Dong-A University Department of Preventive Medicine, School of Medicine, Busan, [4]Department of Internal Medicine, Dong-A University College of Medicine, Busan, [5]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [6]Department of Internal Medicine, Dankook University College of Medicine, Cheonan, [7]Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, [8]Department of Internal Medicine, Institute of Health Science, School of Medicine, Gyeongsang National University, Jinju, and [9]Department of Thoracic and Cardiovascular Surgery, Gyeongsang National University School of Medicine, Jinju, South Korea

*For reprints and all correspondence: Jung-Hun Kang, Department of Internal Medicine, Institute of Health Science, Gyeongsang National University College of Medicine, 79 Gangnam-ro, Jinju 660-702, South Korea. E-mail: newatp@naver.com

[†]These authors contributed equally to this work.

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Abstract

Background: Although chemotherapy is widely recommended for patients with metastatic biliary tract cancer, the natural course of these patients, especially those with good performance status who are indicated for chemotherapy, is not known.

Methods: We retrospectively reviewed patients with metastatic or locally advanced biliary cancer who were diagnosed at six cancer centers. Patients were eligible if they had good performance (ECOG 0–2) and no history of any treatment for cancer. The primary objective was to evaluate the survival time of patients with advanced biliary cancer with good performance who were untreated.

Results: Of the 1677 patients, 204 met the inclusion criteria. The median age and overall survival were 72.0 years and 7.1 months. Overall survival (months) by location was 4.7 for intrahepatic, 9.7 for extrahepatic, 4.4 for gallbladder and 11.2 for ampulla of vater cancer. In subgroup analysis, overall survival of locally advanced biliary cancer was 13.8 months and that of patients with normal carcinoembryonic antigen/carbohydrate antigen 19-9 was 10.6 months. In multivariate analysis, variables that were associated with poor prognosis were metastatic biliary cancer [hazard ratio 2.19 ($P = 0.001$)], high baseline carcinoembryonic antigen level (defined as >4.0 ng/ml) [hazard ratio 1.51 ($P = 0.024$)] and high baseline carbohydrate antigen 19-9 level (defined as >100 U/ml) [hazard ratio 1.93 ($P = 0.001$)].

Conclusions: Advanced biliary tract cancer with good performance status showed modest survival without any treatment. Furthermore, subgroup analysis showed that patients with normal carbohydrate antigen19-9 or carcinoembryonic antigen level or locally advanced status had favorable survival. Further studies comparing the outcome of chemotherapy with that of best supportive care in patients with unresectable biliary tract cancer are warranted.

Key words: natural history, biliary tract cancer, best supportive care

Introduction

Biliary tract cancer (BTC) is a rare and genetically heterogeneous cancer characterized by mutated epithelial cells that originate in the bile duct (1). The incidence rate of BTC varies depending on geographic location and BTC is more common in developing areas such as Asia and Latin America but rare in western countries (2,3). BTCs, which include gallbladder (GB) cancer, ampulla of Vater (AoV) cancer and intrahepatic and extrahepatic cholangiocarcinoma, are unfortunately known to have poor prognosis. Although there are data supporting gemcitabine-based chemotherapy in patients with metastatic BTC (4–6), the evidence for a clinical benefit of chemotherapy in these groups is far from conclusive. Sharma et al. (7) reported that gemcitabine-based chemotherapy was superior to best supportive care (BSC) in GB cancer. However, these studies were underpowered by the small number of patients in the BSC arm ($n = 28–45$) and the cancer type was limited to only GB cancer or mixed BTC and pancreatic cancer. Thus, it is hard to generalize the effect of chemotherapy to all cases of advanced BTC.

National Comprehensive Cancer Network (NCCN) guidelines recommend BSC as an option for metastatic BTC. However, little is known about the natural course of untreated BTC and prospective cohort studies on this subject are extremely difficult because of the rarity of the disease and associated ethical issues. Several retrospective studies that reported the survival of patients with advanced BTC who were given only BSC showed values for overall survival (OS) ranging from 3.1 to 12 months (6–9). These diverse results may result from different study populations including poor performance status (PS) groups or those with localized disease. Considering that chemotherapy is usually indicated for patients with good PS and metastatic stage disease, data on the natural course of untreated BTC could be also hard for physicians to interpret. Physicians usually select supportive care rather than chemotherapy in patients with BTC who have poor PS. When data are analyzed by simply categorizing patients into BSC and chemotherapy groups the results could be significantly distorted by selection bias. Furthermore, in our experience metastatic BTC has various clinical courses and some patients live for a long time without any treatment for the cancer. Therefore, survival data of patients with BTC who are eligible for chemotherapy are urgently needed. To our knowledge, there is no study on the natural history of patients with metastatic BTC with good PS. The objective of this study was to evaluate the natural history of metastatic BTC, i.e. survival of patients with BTC who are eligible for chemotherapy but did not receive any treatment for their cancer.

Patients and methods

Study population and design

This retrospective study was conducted from 2005 to 2013 at six cancer centers in Korea. We selected patients with advanced BTC who met the following criteria for inclusion in this study: (i) histologic diagnosis of locally advanced or metastatic BTC (intrahepatic or extrahepatic cholangiocarcinoma, GB cancer or AoV cancer) and (ii) ECOG PS of 0–2. Exclusion criteria included patients who had undergone curative surgery, chemotherapy or radiation therapy for BTC, resectable BTC or ECOG PS of 3 or 4. Enrolled patients were classified by several variables and their survival time was analyzed. Demographic information including gender, age, cancer extent and location, survival data and laboratory results were collected. Continuous variables were dichotomized using the following cutoffs: age, 70 years; white blood cell count (WBC), 10 000/μl; hemoglobin (Hb), 11 g/dl; albumin 3.5 g/dl; aspartate aminotransferase–alanine aminotransferase (AST/ALT), 50/50 IU/l; carcinoembryonic antigen (CEA), 4.0 ng/ml and carbohydrate antigen (CA) 19-9, 100 U/ml. Categorical variables were divided as follows: ECOG PS, 0–1 and 2; stage, metastatic disease and locally advanced disease; bile drain, performed and not performed.

The primary objective was to evaluate the survival time of patients with advanced BTC with ECOG PS 0–2. Secondary objectives were to examine survival differences among other variables. The study protocol was approved by the Institutional Review Board.

Statistical analysis

Survival curves and results were estimated with the Kaplan–Meier method and compared using log-rank test. Survival was calculated from the date of diagnosis to date of last follow-up or death. Variables for survival were assessed using multivariate analysis with Cox proportional hazards regression models. All analyses were performed with the Statistical Package for the Social Sciences (SPSS, version 18.0; SPSS software, IBM corp., Armonk, NY, USA).

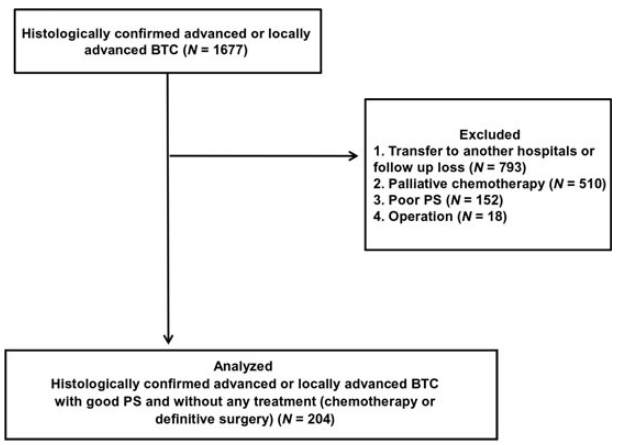

Figure 1. Flow diagram of patient selection.

Results

Demographic and clinical features

Among a total of 1677 cases who meet the eligible criteria selected at the six cancer centers in Korea, 1473 cases were excluded for various reasons and 204 patients were included in our analyses (Fig. 1). The demographic features and survival data of the enrolled patients are summarized in Table 1. The median age was 72.0 years (range: 39–89) and median OS was 7.1 months (range: 0.2–46.9). Of the 204 patients, 123 (60.3%) had ECOG PS 0 or 1. Regarding cancer type, 54 patients (26.5%) had intrahepatic cholangiocarcinoma, 94 (46.1%) had extrahepatic cholangiocarcinoma, 35 (17.1%) had GB cancer and 21 (10.3%) had AoV cancer. At the time of analysis 154 patients had died and 50 were alive.

Survival analysis

Median survival of the total enrolled patient population was 7.1 months (range 0.2–46.9 months). OS was significantly different by cancer location: 4.70 months for intrahepatic, 9.7 months for extrahepatic, 4.4 months for GB cancer and 11.2 months for AoV cancer ($P = 0.015$). Patients with initially metastatic BTC had a poor prognosis with a median OS value of 6.20 months, whereas those with locally advanced BTC had a relatively good prognosis with OS of 13.80 months ($P = 0.001$). Elevated baseline CEA (>4 ng/ml) and CA 19-9 (>100 U/ml) were associated with poor survival, with median survival times of 5.8 months and 6.0 months, respectively, whereas patients with baseline CEA and CA 19-9 within the normal range showed significantly longer median survival (both 10.6 months; $P < 0.01$

Table 1. Patients' demographics

Variables	Median values (min to max) or number	Median OS (95% CI)	*P* value
Age	72.0 years (39–89)		
Overall survival	7.1 months (0.2–46.9)		
Gender			
Male	114	8.30 (6.75–9.85)	0.315
Female	90	5.60 (3.86–7.34)	
Location			
Intrahepatic	54	4.70 (3.54–5.87)	**0.015**
Extrahepatic	94	9.7 (6.49–12.91)	
Gallbladder	35	4.4 (2.90–5.90)	
Ampullary	21	11.2 (5.10–17.30)	
ECOG PS			
0	7	15.50 (0–32.81)	0.101
1	116	7.0 (4.65–9.35)	
2	81	6.5 (4.62–8.34)	
Disease extent			
Locally advanced	41	13.80 (8.35–19.25)	**0.001**
Advanced	163	6.20 (5.34–7.06)	
White blood cell count			
≥10 000/μl	51	6.00 (4.20–7.80)	0.589
<10 000/μl	153	7.60 (6.13–9.07)	
Hemoglobin			
≥11 g/dl	135	7.00 (4.76–9.24)	0.814
<11 g/dl	69	7.50 (5.61–9.39)	
Albumin	3.5 mg/dl (1.0–4.9)		
≥3.5 g/dl	102	6.00 (4.36–7.64)	0.122
<3.5 g/dl	102	8.90 (5.86–11.94)	
Aspartate transaminase			
≥40 IU/l	107	8.20 (5.54–10.86)	0.725
<40 IU/l	97	6.60 (5.11–8.01)	
Alanine aminotransferase			
≥40 IU/l	96	8.40 (5.87–10.93)	0.863
<40 IU/l	108	6.30 (5.62–7.98)	
Bilirubin	1.2 mg/dl (0.2–36.9)		
≥1.2 mg/dl	102	9.50 (7.57–11.43)	0.091
<1.2 mg/dl	102	5.6 (4.35–6.86)	
Bile drain			
Performed	126	8.30 (6.18–10.42)	0.357
Not performed	77	6.20 (4.57–7.83)	
Unknown	1		
Carcinoembryonic antigen (CEA)	4.6 ng/ml (0.4–1449.0)		
≥4 ng/ml		5.80 (4.62–6.98)	**0.006**
<4 mg/ml		10.60 (7.26–13.94)	
Carbohydrate antigen (CA) 19-9	160.4 U/ml (1.0–140 000.0)		
≥100 U/ml		6.00 (5.16–6.84)	**0.001**
<100 U/ml		10.60 (5.86–15.34)	

The bold values indicate statistically significant factors.

Table 2. Multivariate analysis for survival times among variables

	Hazard ratio (95% CI)	*P* value
Age		
≥70	1.08 (0.75–1.54)	0.681
<70	1.00	
Gender		
Female	1.08 (0.76–1.55)	0.665
Male	1.0	
Stage		
Metastatic	2.19 (1.39–3.45)	**0.001**
Locally advanced	1.00	
CEA		
≥4.0	1.51 (1.06–2.17)	**0.024**
<4.0	1.00	
CA 19-9		
≥100.0	1.93 (1.33–2.81)	**0.001**
<100	1.00	

The bold values indicate statistically significant factors.

compared with patients with elevated values). A better PS tended to be associated with a longer survival time, but because of the small number of patients with PS 0 the difference was not statistically significant (PS 0, 15.5 months; PS 1, 7.0 months and PS 2, 6.5 months, $P = 0.101$). The median survival times for other variables (age, gender, WBC, Hb, albumin, AST, ALT and bile drain) are summarized in Table 1. *P* values <0.05 were considered significant and there were no statistically significant differences among these variables.

Prognostic significance of variables

In multivariate analysis, variables that were associated with poor prognosis were disease extent (metastatic disease) [hazard ratio (HR) 2.19 (95% confidence interval, CI 1.39–3.45 $P = 0.001$)], high baseline CEA level (defined >4.0 ng/ml) [HR 1.51 (95% CI 1.06–2.17 $P = 0.024$)] and high baseline CA 19-9 level (defined as >100 U/ml) [HR 1.93 (95% CI 1.33–2.91 $P = 0.001$)].

The results are summarized in Table 2.

Discussion

In this study, we analyzed the OS of patients with BTC with good PS when they did not receive any treatment for the primary cancer. The natural course of patients with BTC with good PS was OS of 7.1 months. This survival time is somewhat disappointing result in comparison with the historical data for patient receiving chemotherapy; however, patients in specific groups revealed more favorable survival (13.8 months for those with locally advanced disease and 10.6 months for those with normal baseline CEA and CA 19-9). Although previous studies occasionally reported the natural course of BTC for patients who are eligible for chemotherapy, these studies were limited by small sample size ($N = 27$) or inclusion of patients with pancreatic cancer or poor PS (4,7,9). According to reported data, the median OS of patients with untreated BTC who were fit for palliative chemotherapy ranged for 2.5–4.5 months. However, as mentioned previously, it is hard to generalize reported outcomes for predicting the prognosis of patients with BTC receiving BSC. Our study overcame the shortcomings of previous studies. In addition to the homogeneity of cancer type and PS, the number of patients in our cohort ($N = 204$) was the largest among studies in this field.

Based on the results of a randomized Phase III trial, combination chemotherapy with gemcitabine plus platinum became the widely

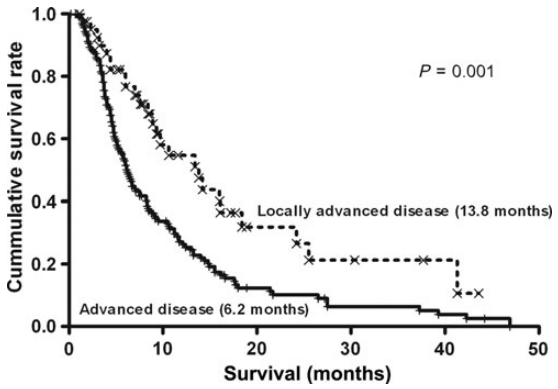

Figure 2. Kaplan–Meier estimate of overall survival (OS) for locally advanced disease and advanced disease with BTC.

recommended regimen for unresectable BTC. The enrolled population and prognosis of the patients in that trial were similar to those for specific groups of our study (10). OS in the Phase III trial was 11.7 months for the gemcitabine–cisplatin arm. The prognosis was similar to that of subgroups in our study with locally advanced stage (13.8 months), normal CEA (10.6 months) or normal CA 19-9 (10.6 months). The results of our study raise the issue of the role of palliative chemotherapy in patients with BTC who have favorable prognostic factors. A randomized Phase III comparing chemotherapy with BSC would be the best approach to address this debatable issue. However, such a study would take a long time and it would be hard to recruit patients. Alternative methods such as using statistical techniques to compare the prognosis of two groups could also be considered.

The OS of the subgroup of patients with good prognostic factors (i.e. locally advanced disease and/or normal CEA/CA 19-9) in our study was comparable with that of patients with advanced BTC who received chemotherapy. In the only Phase III trial (10), the median survival was 11.7 months in the gemcitabine–cisplatin group and 8.1 months in the gemcitabine arm. Other studies that targeted patients with advanced BTC who were given palliative chemotherapy showed a median OS of 5.1–15.4 months, 5.1–12.4 months for 5-FU-based regimens (11–15) and 8.4–15.4 months for gemcitabine-based regimens (5,16–18).

There are several studies on prognostic factors that affect survival in BTC. In particular, CA 19-9 level has been actively studied. Harder et al. reported that baseline CA 19-9 level has prognostic relevance in advanced BTC and proposed a cutoff level of 300 U/ml for CA 19-9 (19). Liu et al. reported a meta-analysis of the prognostic value of CA 19-9 in cholangiocarcinoma. Nine studies were analyzed and the meta-analysis showed that elevation of pretreatment CA 19-9 levels was correlated with poor prognosis (20). In addition to baseline CA 19-9 levels, Park et al. (21) reported other prognostic factors in patients with advanced biliary tract adenocarcinoma. As independent prognostic factors, metastatic disease (HR 1.521), intrahepatic cholangiocarcinoma (HR 1.368), liver metastasis (HR 1.845), ECOG PS (HR 1.707) and alkaline phosphatase level (HR 1.001) were statistically significant. As long-term survival can be expected in patient groups with these good prognostic factors, differentiated studies of subgroups will be needed for treatment decisions in patients with advanced BTC.

There are several limitations in our study. First, data collection in this study was by retrospective chart review and therefore does not reflect subjective information and several laboratory findings that had not been documented in the charts. Previously known prognostic

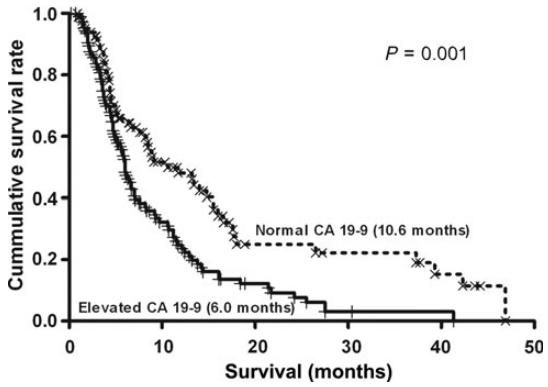

Figure 3. Kaplan–Meier estimate of OS for normal CA 19-9 and elevated CA 19-9 with biliary tract cancer.

factors such as C-reactive protein, lactic dehydrogenase and ALP could not be included in our analysis. Next, our study population included all types of BTC including GB cancer, which has a relatively poor prognosis. In an analysis limited to GB cancer, Sharma et al. (7) reported a randomized study that compared efficacy and survival between BSC and chemotherapy in patients with GB cancer with ECOG PS 0–2. Although the study included a small number of patients, survival was superior in the chemotherapy groups (4.5, 4.6 and 9.5 months for BSC, FUFA and modified gemcitabine combined with oxaliplatin (GEMOX), $P = 0.039$). It seems that GB cancer has an extremely poor prognosis regardless of PS. Consistent with this, the median survival of patients with GB cancer in our study was only 4.4 months. Older median age of our study could be another bias. (75 years for our study versus 51 years of BSC group, 47 years of FUFA group and 49 years of modified GEMOX group for Sharma's study) Though it was not statistically significant difference for prognosis, the median age of our study patients was 72.0 years which is ~10 years older than the existing reference studies for BTC.

In conclusion, patients with metastatic BTC with good PS who had not undergone any treatment for their primary cancer showed modest survival. Notably, patients with normal CEA and/or CA19-9 level or locally advanced status showed favorable survival. Further comparative prospective cohort studies will be aided to justify the use of chemotherapy in patients with unresectable BTC and a good PS.

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Conflict of interest statement

None declared.

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