Gemcitabine Plus Cisplatin Chemotherapy Prolongs the Survival in Advanced Hilar Cholangiocarcinoma

A Large Multicenter Study

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Objectives: Gemcitabine plus cisplatin (GC) is recommended as first-line treatment for advanced cholangiocarcinoma. We investigated the impact of GC in patients with unresectable hilar cholangiocarcinoma (HC) based on the time taken for effective biliary drainage (EBD).

Materials and Methods: We retrospectively enrolled 113 patients with unresectable HC. Thirty-nine and 74 patients received GC chemotherapy and best supportive care (BSC), respectively. EBD was defined as a reduction in total bilirubin $>50\%$ or to a value <2 mg/dL after the drainage procedure. Early EBD (eEBD) and delayed EBD (dEBD) were separated by 2 weeks. Overall survival (OS) was estimated.

Results: The GC group showed a significantly longer median OS than the BSC group (12.8 vs. 6.1 mo; $P<0.001$). Moreover, the eEBD group experienced a significantly longer OS than the dEBD group (8.2 vs. 4.3 mo; $P<0.001$). GC led to improved OS in the eEBD (12.8 vs. 6.8 mo; $P=0.003$) and dEBD (12.2 vs. 3.4 mo; $P=0.009$) groups. In multivariate analysis, dEBD (adjusted hazard ratio [aHR], 1.785; 95% confidence interval [CI], 1.183-2.691; $P=0.006$), BSC (aHR, 2.409; 95% CI, 1.579-3.675; $P<0.001$), and an ECOG status ≥ 2 (aHR, 3.721; 95% CI, 2.093-6.615; $P<0.001$) were associated with poor prognosis. In GC group, the older (70 y and above) patients did not have a higher risk of death than younger patients.

Conclusions: GC prolongs the survival of patients with unresectable HC, even those with dEBD or elderly.

Key Words: gemcitabine plus cisplatin, hilar cholangiocarcinoma, effective biliary drainage, overall survival

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This study adhered to ethical principles regarding medical research involving human subjects in accordance with the Declaration of Helsinki. Furthermore, this study, which aspired to protect the lives, health, privacy, and dignity of the participants, was approved by the appropriate Medical Ethics Committee.

D.W.S. and M.J.K.: analyzed the data and drafted the article. J.-H.H.: designed the study and edited the manuscript. J.-c.L.: performed data handling and statistical analysis. J.K., S.M.W., W.J.L., and K.H.L.: contributed to the review of the manuscript.

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Hilar cholangiocarcinoma (HC), or Klatskin tumor, originates from the confluence of the right and left intrahepatic bile ducts and accounts for ~50% of all biliary tract cancers (BTCs). The only curative treatment for HC is margin-negative surgical resection, and R0-resected HC has median survival of 30 months, and 5-year survival of 30%.[1] However, many perihilar tumors are not resectable and palliative chemotherapy is the most important treatment with the potential to prolong life.[2] The Advanced Biliary Cancer (ABC)-02 trial, published in 2010, demonstrated the survival benefit of gemcitabine plus cisplatin (GC) chemotherapy over gemcitabine monotherapy in patients with advanced BTC (11.7 vs. 8.1 mo; $P<0.001$).[3] Since then, GC has been used as the first-line standard chemotherapy for unresectable HC. In ABC-02 trial, however, only 57 (13.9%) patients with HC were included, and GC chemotherapy did not exhibit a survival benefit over gemcitabine monotherapy in the HC subgroup.[3] Moreover, several previous studies on chemotherapy for unresectable cholangiocarcinoma included not only HC but also intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary carcinoma.[4–7] There have been no previous studies analyzing the effects of GC chemotherapy on HC alone.

Unlike other BTCs, cholestasis due to malignant stricture is very common, and biliary drainage is mandatory for symptom relief or subsequent chemotherapy in HC patients. Successful biliary drainage is known to improve survival.[8–15] However, it is not easy to resolve cholestasis completely in spite of performing multiple stenting via per-oral and percutaneous approaches, especially among patients with advanced HC. In clinical situations, many physicians hesitate to start chemotherapy, unless cholestasis resolves completely or almost completely. Moreover, doctors are reluctant to start chemotherapy if the patient is elderly or takes a long time to achieve effective biliary drainage (EBD). For these reasons, fewer patients with advanced HC have a chance to receive chemotherapy compared with patients with other types of BTCs.

The purpose of this study was to analyze the effect of GC chemotherapy in both early and delayed EBD (eEBD and dEBD, respectively) groups. The prognostic factors affecting the survival of unresectable HC patients were also evaluated.

MATERIALS AND METHODS

Patients and Data Collection

We retrospectively analyzed the medical records of patients diagnosed with unresectable HC from 2010 to 2016 at the following 3 tertiary referral hospitals in Korea: Seoul National University Bundang Hospital (SNUBH); Samsung Medical Center (SMC); and National Cancer Center (NCC). The data used in this study included information on demographic, radiologic, and pathologic characteristics; blood test results; biliary drainage procedures (endoscopic vs. percutaneous); and death. Informed consent was waived because of

the retrospective nature of the study and the analysis used anonymous clinical data. This study was approved by the Institutional Review Boards of the 3 institutions (SNUBH Medical Ethics: B-1905/540-108; SMC Medical Ethics: SMC 2019-05-019-001; and NCC Ethics Committee: NCC2018-0168).

The inclusion criteria were as follows: (a) pathologically proven and radiologically unresectable HC as determined by a multidisciplinary tumor board; (b) patients who underwent a biliary drainage procedure either via an endoscopic or percutaneous approach; (c) adults over 18 years of age; and (d) patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. The exclusion criteria were as follows: (a) pathologically unproven HC; (b) intrahepatic cholangiocarcinoma, distal bile duct cancer, gallbladder cancer, ampullary carcinoma, or recurred cholangiocarcinoma; (c) patients receiving first-line chemotherapy or radiotherapy other than GC chemotherapy; (d) patients who did not undergo a biliary drainage procedure; (e) patients who did not achieve EBD.

Definitions of EBD

EBD was defined as a reduction in serum total bilirubin $>50\%$ or to a value <2.0 mg/dL after the drainage procedure. The eEBD and dEBD were separated by 2 weeks. Preprocedural total bilirubin was defined as the highest value within 1 week before the procedure. The biliary drainage procedure refers to the following: (1) insertion of an endoscopic retrograde biliary drainage stent or an endoscopic nasobiliary drainage catheter using endoscopic retrograde cholangiopancreaticography; and (2) percutaneous transhepatic biliary drainage (PTBD).

Chemotherapy Regimen and Treatment Response Assessment

In the GC group, chemotherapy was performed with cisplatin (25 mg per square meter of body surface area) followed by gemcitabine (1000 mg per square meter of body surface area), each administered on days 1 and 8, every 3 weeks. Tumor response was assessed every 3 cycles using computed tomography and graded according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[16] If the tumor did not show evidence of progression on the ninth week (3 cycles) computed tomography scan, another 3 cycles of the same regimen were administered until progression or development of intolerance was observed. Patients in the best supportive care (BSC) group received only conservative treatment to relieve symptoms without chemotherapy or radiation therapy.

Statistical Analyses

Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as frequencies and proportions. Continuous variables with normal distributions were analyzed using Student *t* tests. The overall survival (OS) was calculated from the date of pathologic diagnosis to death or the last follow-up date. OS was estimated using the Kaplan-Meier survival curves and compared via the log-rank test. Cox proportional hazards regression models were used to determine the association between patient characteristics and OS. All statistical analyses were performed using IBM SPSS, version 22 for Windows (IBM Inc., Armonk, NY) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org). A two-sided P-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

From 2010 to 2016, 121 patients were diagnosed with pathologically proven and unresectable HC at 3 tertiary referral hospitals in Korea (Fig. 1). Among them, the following 8 patients were excluded: (a) 4 patients who underwent drainage procedures after GC chemotherapy; (b) 3 patients who did not undergo a biliary drainage procedure; and (c) 1 patient who received gemcitabine monotherapy. Finally, the clinical data of 113 patients with unresectable HC were reviewed. Of these, 76 were in the eEBD group and 37 were in the dEBD group. A total of 39 patients (33 in the eEBD group and 6 in the dEBD

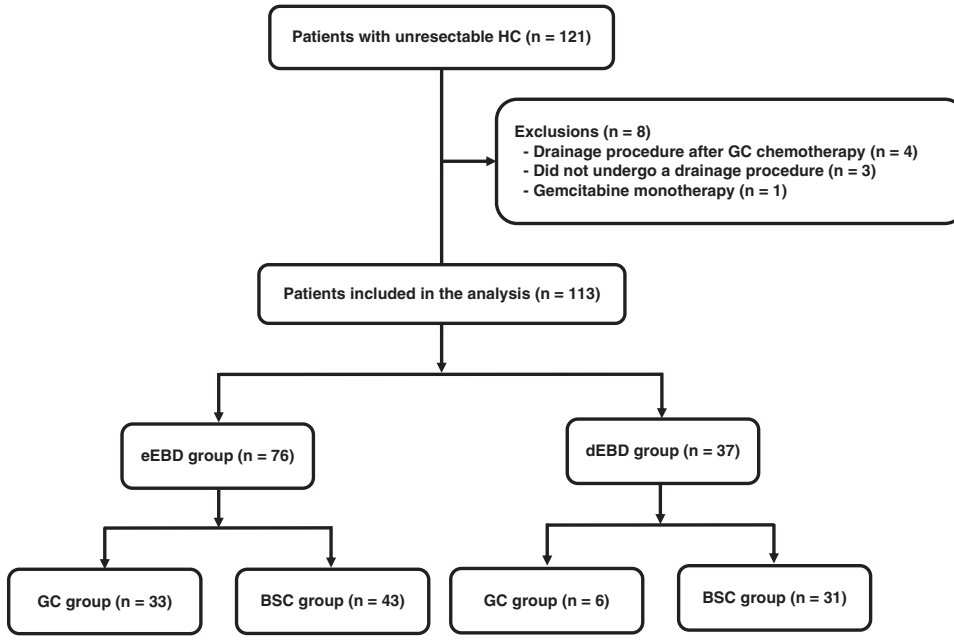

FIGURE 1. Flowchart of the study. BSC indicates best supportive care; dEBD, delayed effective biliary drainage; eEBD, early effective biliary drainage; GC, gemcitabine plus cisplatin; HC, hilar cholangiocarcinoma.

group) and 74 patients (43 in the eEBD group and 31 in the dEBD group) received GC chemotherapy and BSC only, retrospectively.

The baseline patient characteristics are summarized in Table 1. Patients in the BSC group were significantly older than those in the GC chemotherapy group (73.4 vs. 65.5 y; $P < 0.001$). There were no differences between the 2 groups in terms of sex, ECOG performance status, number of metastatic sites, CA19-9 level, and Bismuth type. The total bilirubin at initial diagnosis was higher in the BSC group than in the GC group; however, this difference was not significant (12.9 vs. 9.9 mg/dL; $P = 0.073$). On average, patients in the GC group received 6 cycles (range, 1 to 15) of chemotherapy.

Survival Analysis

Table 2 shows the OS of patients in each group. The median OS was significantly longer in the GC chemotherapy group than in the BSC group (12.8 vs. 6.1 mo; $P < 0.001$) (Fig. 2A). In addition, the eEBD group had significantly longer survival than the dEBD group (8.2 vs. 4.3 mo; $P < 0.001$) (Fig. 2B). Patients receiving GC chemotherapy in the eEBD group experienced longer survival than those in the BSC group (12.8 vs. 6.8 mo; $P = 0.003$) (Fig. 2C). Furthermore, patients receiving GC chemotherapy in the dEBD group had significantly longer survival than those in the BSC group (12.2 vs. 3.4 mo; $P = 0.009$) (Fig. 2D). In the GC chemotherapy group, there was no difference in survival based on the time required to achieve EBD (eEBD, 12.8 mo vs. dEBD, 12.2 mo; $P = 0.684$). Conversely, in the BSC group, the survival was longer in the eEBD group than in the dEBD group (eEBD, 6.8 mo vs. dEBD, 3.4 mo; $P = 0.004$).

TABLE 1. Baseline Characteristics of the Patients

	n, N (%)			
Variables	GC Group (n = 39)	BSC Group (n = 74)	Total (N = 113)	*P*
Age, median (y)	65.5 ± 10.6	73.4 ± 9.3	70.7 ± 10.4	< 0.001
< 70	21 (53.8)	21 (28.4)	42 (37.2)	0.014
≥ 70	18 (46.2)	53 (71.6)	71 (62.8)	
Sex				0.695
Male	28 (71.8)	49 (66.2)	77 (68.1)	
Female	11 (28.2)	25 (33.8)	36 (31.9)	
ECOG				0.263
0	14 (35.9)	21 (28.4)	35 (31.0)	
1	22 (56.4)	39 (52.7)	61 (54.0)	
2	3 (7.7)	14 (18.9)	17 (15.0)	
No. metastatic sites				0.197
0	24 (61.5)	53 (71.6)	77 (68.1)	
≥ 1	15 (38.5)	21 (28.4)	36 (31.9)	
CA19-9 (U/mL)				1.000
Normal (< 37)	6 (15.4)	10 (13.5)	16 (14.2)	
Elevated (≥ 37)	33 (84.6)	64 (86.5)	97 (85.8)	
Bismuth type				0.322
I	2 (5.1)	3 (4.0)	5 (4.4)	
II	1 (2.6)	7 (9.5)	8 (7.1)	
III	12 (30.8)	26 (35.1)	38 (33.6)	
IV	24 (61.5)	38 (51.4)	62 (54.9)	
Total bilirubin (mg/dL)	9.9 ± 8.6	12.9 ± 8.3	11.9 ± 8.5	0.073
EBD (wk)				0.001
Early (< 2)	33 (84.6)	43 (58.1)	76 (67.3)	
Delayed (≥ 2)	6 (15.4)	31 (41.9)	37 (32.7)	

Data are presented as mean ± SD or numbers and proportions.

BSC indicates best supportive care; CA19-9, carbohydrate antigen 19-9; EBD, effective biliary drainage; ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine plus cisplatin.

Prognostic Factors Affecting Survival

Univariate and multivariate analysis showed that dEBD (adjusted hazard ratio [aHR], 1.785; 95% confidence interval [CI], 1.183-2.691; $P = 0.006$), BSC without chemotherapy (aHR, 2.409; 95% CI, 1.579-3.675; $P < 0.001$), and an ECOG status ≥ 2 (aHR, 3.721; 95% CI, 2.093-6.615; $P < 0.001$) were significantly associated with poor prognosis (Table 3). Conversely, older (≥ 70 y) patients did not have a higher risk of death than younger patients (aHR, 1.064; 95% CI, 0.718-1.577; $P = 0.757$). Patients in the GC chemotherapy group (both older and younger) showed longer survival than those in the BSC group (Fig. 3).

DISCUSSION

Cholangiocarcinoma encompasses all tumors originating from the epithelium of the bile duct. In 2019, it was estimated that 12,360 people would be diagnosed with BTCs and that there would be ~3960 deaths from BTCs in the United States.[17] Despite the pharmacological and technical advances in cancer treatment, the prognosis for BTC is still poor.[18,19]

Until the introduction of GC chemotherapy in 2010,[3] many patients with advanced HC only received biliary decompression procedures and BSC as there were no effective chemotherapeutic regimens.[20,21] A randomized, controlled, ABC-02 trial of the United Kingdom National Cancer Research Institute and a randomized phase II study in Japan showed that patients with advanced BTC who received GC chemotherapy had improved survival compared with the patients who received gemcitabine alone.[3,22] On the basis of these findings, GC chemotherapy has been considered the standard first-line treatment for advanced BTC. However, these 2 studies included all types of BTC (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma). Moreover, the ABC-02 trial did not show the superiority of GC chemotherapy over gemcitabine alone in HC. Unlike the other BTCs, advanced HC patients inevitably face high-level biliary obstruction, which can sometimes cause unresolved cholestasis and uncontrolled biliary infection. In turn, patients do not have a chance to receive subsequent chemotherapy, thus leading to shortened survival. Our study demonstrated that the median OS of the GC group was 12.8 months, similar to the 11.7 months previously shown by Valle et al[3] in pathologically proven unresectable HC patients. The survival time was doubled in the GC group compared with that in the BSC group (12.8 vs. 6.1 mo; $P < 0.001$). In addition, these survival benefits of chemotherapy remained among dEBD and elderly (70 y and above) patients.

Patients with unresectable or metastatic HC should be considered for biliary drainage using an endoscopic retrograde cholangiopancreaticography or PTBD approach. The complex biliary strictures of HC present significant challenges for providing long-lasting and adequate biliary drainage. It is difficult to completely resolve cholestasis, even after repeated interventions via per-oral or PTBD approaches. However, several studies have reported that patients with successful bile drainage show longer survival than patients with failed EBD.[8,10–15] If cholestasis persists despite biliary decompression, doctors usually face the dilemma whether or when to start chemotherapy. However, most of the studies regarding HC

TABLE 2. The Median Overall Survival Based on the Time Taken to Achieve Effective Biliary Drainage in the Gemcitabine Plus Cisplatin Chemotherapy and Best Supportive Care Groups

	GC Group (n = 39)		BSC Group (n = 74)		Total (N = 113)		
Variable	**n**	**Median OS (95% CI) (mo)**	**n**	**Median OS (95% CI) (mo)**	**n**	**Median OS (95% CI) (mo)**	***P***
eEBD	33	12.8 (10.5-15.1)	43	6.8 (6.0-7.7)	76	8.2 (6.1-10.3)	0.003
dEBD	6	12.2 (2.6-21.7)	31	3.4 (1.8-4.9)	37	4.3 (2.3-6.4)	0.009
Total	39	12.8 (11.3-14.3)	74	6.1 (4.9-7.3)	113	7.7 (6.5-8.8)	< 0.001
P		0.684		0.004		< 0.001	

BSC indicates best supportive care; CI, confidence interval; dEBD, delayed effective biliary drainage; eEBD, early effective biliary drainage; GC, gemcitabine plus cisplatin; OS, overall survival.

have evaluated biliary decompression itself. Specifically, studies have evaluated which segment should be drained or which methods should be used, however, they have not focused on chemotherapy because most studies were conducted before the introduction of GC chemotherapy.[8–10] In addition, there have been no studies on whether the time it takes to improve

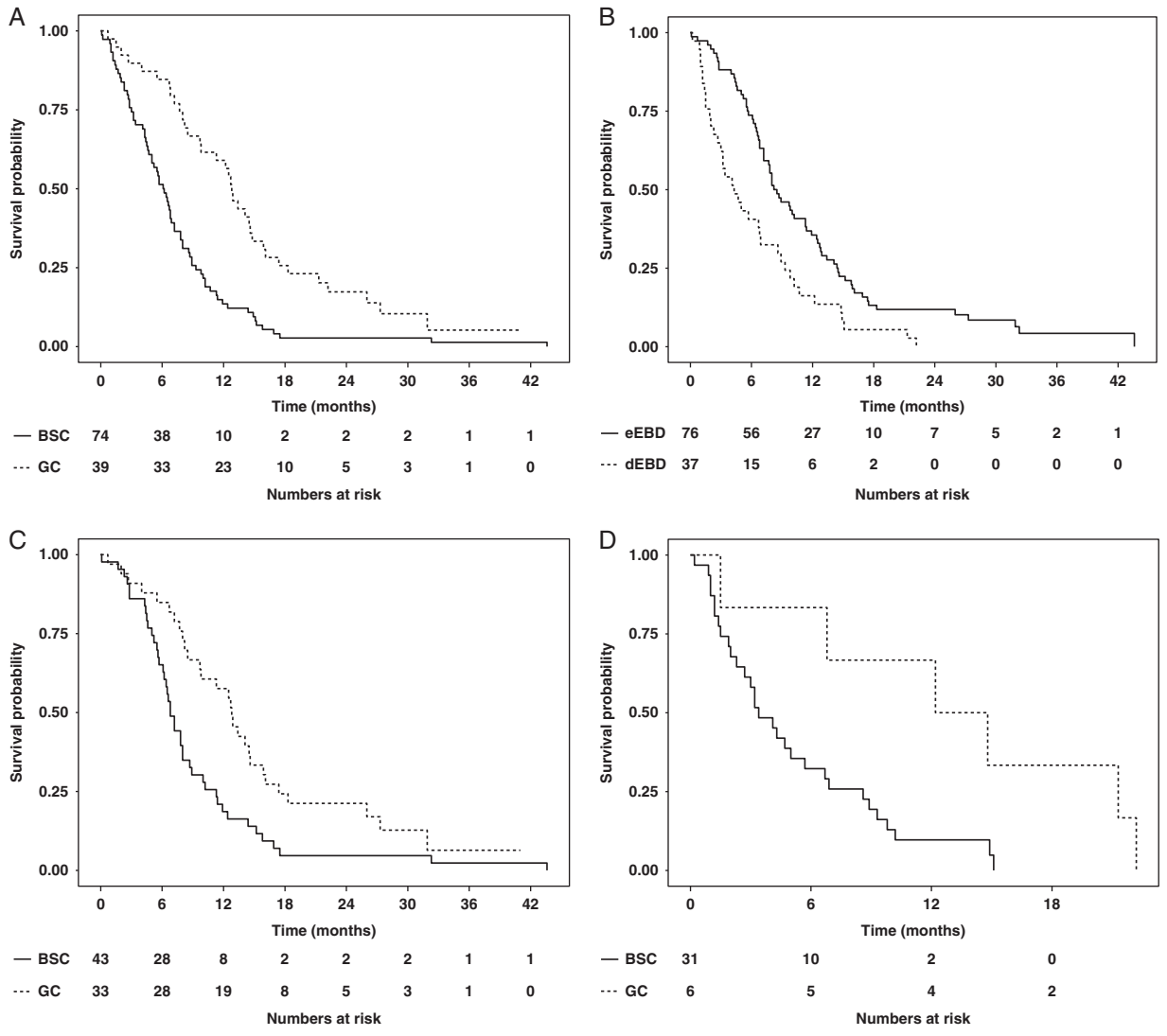

FIGURE 2. Kaplan-Meier curve showing overall survival. A, Comparison of the gemcitabine plus cisplatin chemotherapy group with best supportive care group among all patients. B, Comparison of early effective biliary drainage and delayed effective biliary drainage groups among all patients. C, Comparison of gemcitabine plus cisplatin chemotherapy and best supportive care in the early effective biliary drainage group. D, Comparison of gemcitabine plus cisplatin chemotherapy and best supportive care in the delayed effective biliary drainage group. BSC indicates best supportive care; dEBD, delayed effective biliary drainage; eEBD, early effective biliary drainage; GC, gemcitabine plus cisplatin.

TABLE 3. Univariate and Multivariate Analyses of Overall Survival Among Patients With Unresectable Hilar Cholangiocarcinoma

	Univariate Analysis			Multivariate Analysis		
Variables	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Age, median (y)						
<70		1 (reference)				
≥70	1.064	0.718-1.577	0.757			
EBD (wk)						
Early (<2)		1 (reference)			1 (reference)	
Delayed (≥2)	2.025	1.351-3.036	<0.001	1.785	1.183-2.691	0.006
Chemotherapy						
Yes (GC)		1 (reference)			1 (reference)	
No (BSC)	2.527	1.668-3.831	<0.001	2.409	1.579-3.675	<0.001
ECOG						
0-1		1 (reference)			1 (reference)	
2	3.720	2.123-6.516	<0.001	3.721	2.093-6.615	<0.001
No. metastatic sites						
0		1 (reference)				
≥1	1.391	0.927-2.089	0.111			
CA19-9 (U/mL)						
Normal (<37)		1 (reference)				
Elevated (≥37)	1.571	0.872-2.833	0.134			

aHR indicates adjusted hazard ratio; BSC, best supportive care; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; EBD, effective bile drainage; ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine plus cisplatin; HR, hazard ratio.

cholestasis affects survival. In this study, we showed that GC chemotherapy confers survival benefits in unresectable HC patients in both the eEBD and dEBD groups. In addition, the patients who achieved EBD within 2 weeks had a longer survival than those who did not (eEBD, 8.2 mo vs. dEBD, 4.3 mo; $P < 0.001$). In the eEBD group, the GC group showed a longer survival than the BSC group (GC with eEBD 12.8 mo vs. BSC with eEBD 6.8 mo; $P = 0.003$). Even among those for whom it took >2 weeks to achieve EBD, GC chemotherapy still exhibited a survival benefit (GC with dEBD 12.2 mo vs. BSC with dEBD 3.4 mo; $P = 0.009$). In the GC chemotherapy group, there was no significant difference in the survival time based on the time taken to achieve EBD (GC with eEBD 12.8 mo vs. GC with dEBD 12.2 mo; $P = 0.684$). However, for patients who did not receive chemotherapy for any reason, achieving EBD within 2 weeks prolonged their survival (BSC with eEBD 6.8 mo vs. BSC with dEBD 3.4 mo; $P = 0.004$). Therefore, regardless of the time taken to achieve EBD, GC chemotherapy should be considered as it extends the survival of patients with unresectable HC. If GC chemotherapy is not available for any reason, clinicians should attempt to achieve EBD as soon as possible to improve the patients' prognosis.

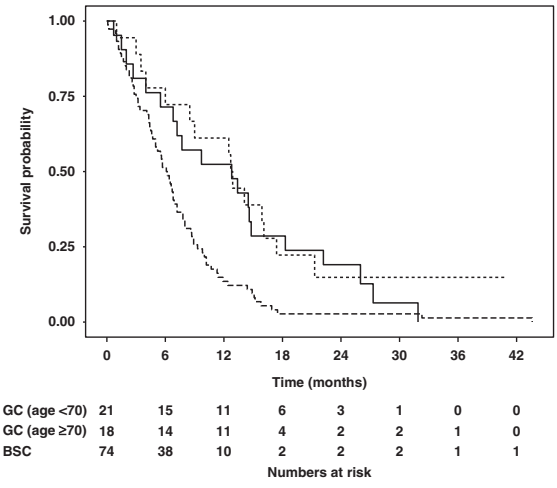

FIGURE 3. Kaplan-Meier curve comparing the survival of gemcitabine plus cisplatin chemotherapy group (dividing older [70 y and above] and younger [younger than 70 y] patients) and BSC group. BSC indicates best supportive care; GC, gemcitabine plus cisplatin

As life expectancy increased, the number of elderly patients diagnosed with BTC increased significantly. If a patient is old or frail, clinicians may hesitate to perform surgery or chemotherapy. Because of the gradual decrease in physical functional reserves, complications and drug toxicity increase with age. Unfortunately, some elderly people miss the opportunity to receive chemotherapy due to their age. In this study, contrary to the concerns, the GC chemotherapy group showed prolonged survival time compared with the BSC group in terms of elderly (70 y and above) patients. Univariate and multivariate analysis found that dEBD (HR, 1.785), BSC without GC chemotherapy (HR, 2.409), and an ECOG status ≥2 (HR, 3.721) were poor prognostic factors for OS in patients with unresectable HC. If the ECOG status was 0 or 1, old age did not affect the survival time of patients with HC. Therefore, elderly patients with a good performance status (ECOG status, 0-1) need to receive appropriate chemotherapy for prolonged survival.

This study was subject to some limitations. Because of its retrospective nature, selection bias cannot be completely excluded, even though a homogenous population was enrolled. In spite of this limitation, our study will be useful in assisting with decision making regarding whether or when to administer chemotherapy, considering that advanced HC patients are typically elderly and repeated procedures are needed to achieve biliary decompression. Unlike other studies,[5,23,24] we only included patients with pathologically proven advanced HC. Without histologic confirmation, primary sclerosing cholangitis or IgG4-related sclerosing cholangitis might be misdiagnosed as BTC. In addition, to the best of our knowledge, this study analyzed the largest cohort of HC patients to date.

In conclusion, both GC chemotherapy and eEBD are the 2 most important factors that should not be overlooked in the treatment of unresectable HC. In the eEBD and dEBD groups, those who received GC had longer survival than those who received BSC. Among patients who received BSC only, those in the eEBD group had longer survival than those in the dEBD group. In addition, GC chemotherapy should be considered in elderly (older than 70 y) with good performance status.

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