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Clinical outcomes of second-line chemotherapy after gemcitabine and cisplatin plus S-1 treatment for patients with advanced biliary tract cancer in the KHBO1401-3A study

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Abstract. Since the completion of the KHBO1401 study, which evaluated the efficacy of the combination of gemcitabine (GEM) and cisplatin (GC) compared with GC plus S-1 (GCS), GCS has become a standard chemotherapy for patients with advanced biliary tract cancer (BTC). However, there are currently no data revealing second-line therapy options after GCS. The present study aimed to evaluate the survival outcomes of patients receiving second-line chemotherapy for advanced BTC, refractory or intolerant to GCS, using data from the KHBO1401 study. Patients who received a second-line treatment after GCS chemotherapy between July 2014 and February 2016 were retrospectively studied. Overall survival (OS) was calculated from the day of GCS treatment failure or the first day of second-line chemotherapy to the final follow-up date or until death from any cause. Among 83 patients refractory or intolerant to GCS chemotherapy, 51 (61%) received second-line chemotherapy, including GCS (n=8), GC (n=15), GEM (n=6), GEM plus S-1 (GS) (n=4) and S-1 (n=18). The 6- and 12-month OS rates were 66.7 and 44.4%, respectively, following second-line chemotherapy, and 6.3 and 3.1%, respectively, in the best supportive care group (P<0.0001). In addition, the 12- and 24-month OS rates were 59.3 and 36.2%, respectively, in the multidrug chemotherapy group, and 26.9 and 9.0%, respectively, in the single-agent chemotherapy group (P=0.0191). These results suggested that second-line combination chemotherapy is a viable treatment option for patients with advanced BTC that is refractory or intolerant to first-line GCS therapy.

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Introduction

Biliary tract cancer (BTC), including intrahepatic and extrahepatic bile duct, gallbladder, and ampullary cancer, is one of the most aggressive cancer types (1,2). Surgical resection is currently the only curative treatment, but the prognosis is usually poor due to difficulties in early diagnosis and high recurrence rates following resection (3). Therefore, systemic chemotherapy is an important part of the treatment regimen to improve the prognosis for patients with advanced BTC.

A combination of gemcitabine (GEM) and cisplatin (GC) therapy has been considered the first-line standard chemotherapy regimen for advanced BTC, supported by results from the previous ABC-02 trial (4). Another Japanese phase III trial (FUGA-BT) reported that therapy using GEM plus S-1, an oral fluoropyrimidine prodrug therapy, was comparable to GC in terms of overall survival (OS). Thus, GEM plus S-1 (GS) is also considered a standard chemotherapy regimen to treat advanced BTC (5). As a new addition, the Kansai Hepatobiliary Oncology Group (KHBO) recently reported the results of a randomized phase III trial (KHBO1401-MITSUBA; ClinicalTrials.gov identifier, NCT02182778) that compared GEM, cisplatin and S-1 therapy (GCS) with GC in patients with unresectable or recurrent BTC (6). In this trial, GCS demonstrated superior efficacy compared with GC in terms of OS time (median OS, 13.5 months with GCS and 12.6 months with GC; hazard ratio, 0.79; 90% confidence interval, 0.628-0.996; P=0.046). Therefore, GCS may soon be a new standard treatment for patients with advanced BTC.

Despite the advances in chemotherapeutic regimens, there are no standard second-line treatments for advanced BTC. A recent phase III trial (ABC-06 study) showed improved patient survival when patients were treated with folinic acid, fluorouracil and oxaliplatin (FOLFOX) compared with active symptom control (ASC) after progression on GC therapy, but the improvement in median OS time with FOLFOX was modest (6.2 vs. 5.3 months, respectively) (7). The only trials currently reporting results are phase II trials with a limited number of patients (8-10). However, second-line chemotherapies, such as GC, GS, S-1 and GEM, are widely accepted in daily practice in Japan. Second-line chemotherapy is decided based on the regimen received as a first-line therapy. For patients treated with GC, second-line treatment options include S-1 single-agent chemotherapy or GS. However, it is difficult to determine the optimal regimens for patients who receive GCS as a first-line therapy. Thus, the present study aimed to evaluate the clinical outcomes of patients receiving second-line chemotherapy after first-line GCS using data from the KHBO1401 clinical trial.

Patients and methods

Study design and patients. A multicenter, retrospective study was conducted to examine the clinical outcomes of patients receiving second-line chemotherapy after first-line GCS treatment using the KHBO1401 study database (6). Between July 9, 2014, and February 4, 2016, 123 patients received GCS as a first-line treatment in the KHBO1401 trial.

The former KHBO1401 trial was a randomized, open-label, phase III clinical trial conducted to evaluate the superiority of GCS compared with GC therapy in patients with unresectable or recurrent BTC (6). Written informed consent was obtained from all patients. The study was initially approved by the Human Ethics Committee at Yamaguchi University (approval no. H30-199), and it was subsequently approved by the Institutional Review Boards of all participating centers (Osaka International Cancer Institute, Osaka; Osaka University Graduate School of Medicine, Osaka; Hokkaido University Graduate School of Medicine, Hokkaido; Wakayama Medical University, Wakayama; Kyoto University Hospital, Kyoto; Tohoku University Hospital, Miyagi; Kumamoto University, Kumamoto; Nihon University School of Medicine, Tokyo; Hyogo College of Medicine, Hyogo; Kindai University Faculty of Medicine, Osaka; Kobe University Hospital and Graduate School of Medicine, Hyogo; University of Tsukuba, Ibaraki; Fukushima Medical University, Aizu Medical Center, Fukushima; Saga University Hospital, Saga; Osaka City General Hospital, Osaka; Yokohama City University, Graduate School of Medicine, Yokohama; Toranomon Hospital, Tokyo; Osaka Rosai Hospital, Osaka; Kobe City Medical Center General Hospital, Kobe; Asahikawa Medical University, Hokkaido; Kansai Rosai Hospital, Hyogo; Tonan Hospital, Hokkaido; National Hospital Organization Osaka National Hospital, Osaka; Nagasaki University Hospital, Nagasaski; Toyonaka Municipal Hospital, Osaka; Kitano Hospital Medical Research Institute, Osaka, Japan). The main eligibility criteria were as follows: Unresectable or recurrent biliary tract cancer, histologically confirmed adenocarcinoma or adenosquamous carcinoma, no prior chemotherapy, age ≥20 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2 (11) and adequate organ function. Exclusion criteria included an age <20 years, prior chemotherapy or radiotherapy (except for adjuvant chemotherapy completed at least 6 months before enrolment) and severe or uncontrolled systemic disease. In the GC group, GEM and cisplatin were administered intravenously at doses of 1,000 and 25 mg/m^2, respectively, on days 1 and day 8, which was repeated every 3 weeks. The total duration of the treatment period was 24 weeks. In the GCS group, GEM and cisplatin were administered intravenously at doses of 1,000 and 25 mg/m^2, respectively, on day 1, and oral S-1 was administered orally twice a day for 7 consecutive days, repeated every 2 weeks. Doses of S-1 were calculated according to body surface area (BSA) as follows: BSA <1.25 m^2, 80 mg/day; 1.25 m^2 ≤ BSA <1.5 m^2, 100 mg/day; and BSA ≥1.5 m^2, 120 mg/day. The protocol was halted before the full 24-week term only if any of the following occurred: Deterioration of general condition due to disease progression, unacceptable or repeated treatment-related toxicity, a >6-week delay in the schedule due to treatment-related toxicity, patient refusal or tumor response allowing potential curative resection.

For the present subgroup analysis, to investigate the clinical outcomes of second-line therapy, patients who were refractory or intolerant to GCS were selected, and the efficacy of second-line regimens was compared with best supportive care (BSC). BSC was defined as analgesics, antibiotics, biliary drainage, transfusions and any other symptomatic treatment. OS time was measured from the first day of second-line chemotherapy or from the day of GCS treatment failure (BSC group) to the final follow-up date or until death from any cause. Progression-free survival (PFS) time was defined as the time from the first day of second-line chemotherapy or from the day of first-line GCS treatment failure (BSC group) to tumor progression or death from any cause.

Second-line regimen. The main regimens were as follows: i) GCS (1,000 mg/m^2 GEM and 25 mg/m^2 cisplatin on day 1,

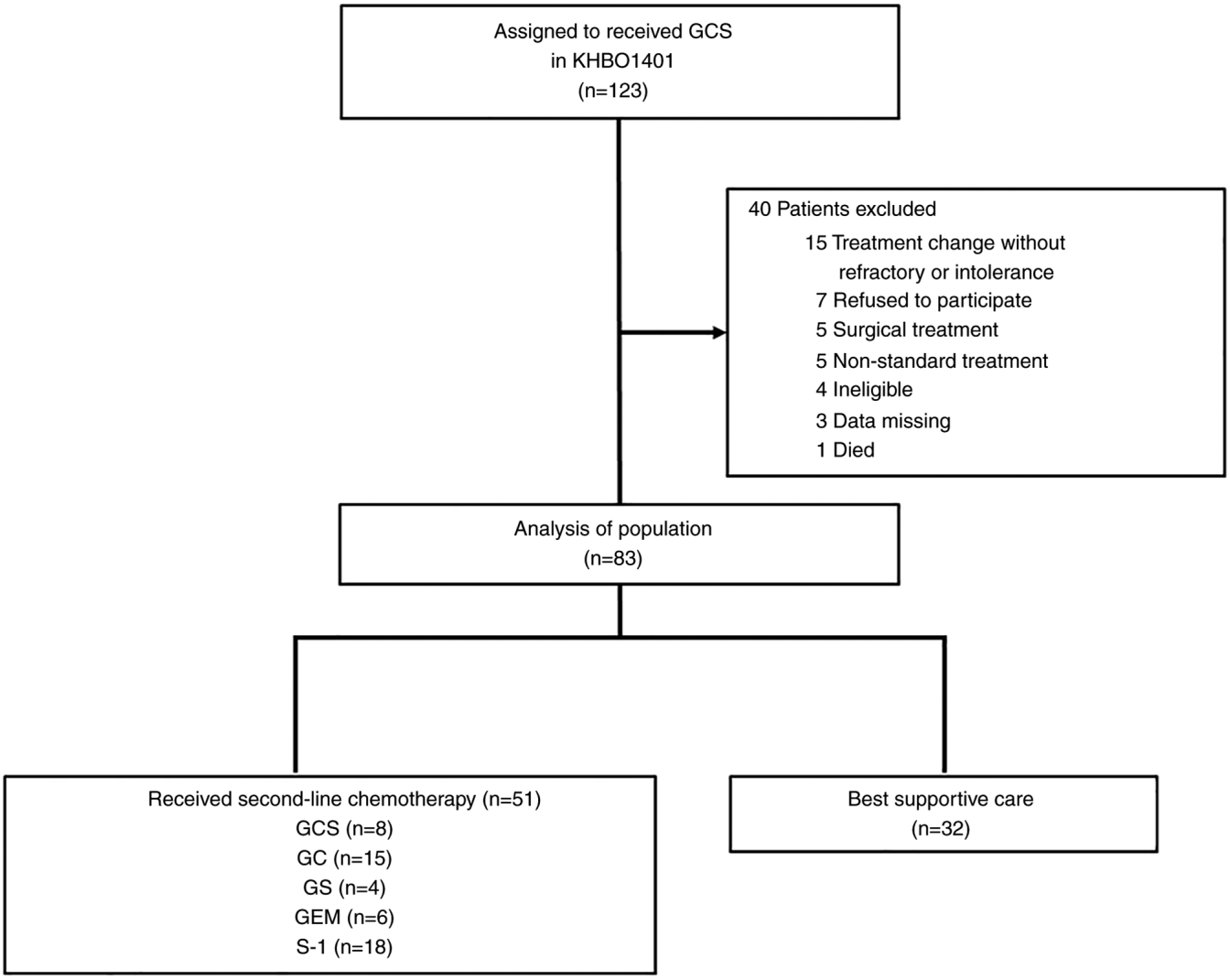

Figure 1. Flow chart of patient therapeutic regimens in the KHBO1401-3A study. GEM, gemcitabine; GC, GEM plus cisplatin; GCS, GC plus S-1.

and oral S-1 twice a day on days 1-7, every 2 weeks); ii) GC (1,000 mg/m^2 GEM and 25 mg/m^2 cisplatin on days 1 and 8, every 3 weeks); iii) GS (1,000 mg/m^2 GEM on days 1 and 8, and oral S-1 twice a day on days 1-14, every 3 weeks); iv) GEM (1,000 mg/m^2 GEM on days 1 and 8, every 3 weeks); and v) S-1 (oral S-1 twice a day on days 1-14, every 3 weeks). Dose reduction and treatment schedule modification for each regimen were considered in cases of adverse events.

Statistical analysis. Quantitative data are expressed as the median (range), and qualitative data are expressed as number and percentage. Categorical variables were compared using the χ^2 and Fisher's exact tests. Mann-Whitney U tests were used to assess differences between the study groups. Survival curves were analyzed using the Kaplan-Meier method and log-rank test or the Gehan-Breslow test. The Benjamini and Hochberg method was applied for multiple comparisons. Statistical analyses were performed using GraphPad Prism V8.0 (GraphPad Software, Inc.) and R version 4.2.1 (The R Foundation for Statistical Computing). P<0.05 was considered to indicate a statistically significant difference.

Results

A total of 83 patients who were refractory or intolerant to first-line GCS treatment, as identified in the trial, were used in the present study. Of these 83 patients, 51 (61%) received second-line chemotherapy (Fig. 1); 8 patients received GCS, 15 received GC, 4 received GS, 6 received GEM and 18 received S-1 therapy. The remaining 32 patients received BSC. The baseline characteristics of the patients are summarized in Table I. There were no significant differences between the study groups in terms of age, sex, primary tumor site, disease stage or GCS duration. However, the number of patients refractory to first-line GCS treatment was higher in the BSC group (P=0.0164). The baseline characteristics of patients who received second-line chemotherapy are summarized in Table II. The majority of patients (90%) had an ECOG-PS score of 0 or 1.

The 6- and 12-month OS rates were 66.7 and 44.4%, respectively, following second-line chemotherapy, and 6.3 and 3.1%, respectively, in the BSC group (P<0.0001) (Fig. 2A). The 6- and 12-month PFS rates were 35.0 and 17.9%, respectively, following second-line chemotherapy, and 6.3 and 3.1%, respectively, in the BSC group (P=0.0363) (Fig. S1).

Table I. Patient characteristics (n=83).

Factors	Second-line chemotherapy (n=51)	Best supportive care (n=32)	P-value
Median age (range), years	67 (39-81)	69 (56-81)	0.4572
Sex, n (%)			>0.9999
Male	28 (55)	18 (56)	
Female	23 (45)	14 (44)	
Primary tumor site, n (%)			0.2166
Gall bladder	13 (25)	15 (47)	
Extrahepatic bile duct	21 (41)	10 (31)	
Intrahepatic bile duct	16 (31)	7 (22)	
Ampullary	1 (2)	0 (0)	
Disease stage, n (%)			0.2778
Unresectable	35 (69)	24 (75)	
Locally advanced	8 (16)	2 (6)	
Metastatic	27 (53)	22 (69)	
Recurrent	16 (31)	8 (25)	
Median GCS duration (range), weeks	22 (0-84)	19 (4-79)	0.4218
GCS duration ≥24 weeks, n (%)	25 (49)	14 (44)	0.6589
Discontinuation of GCS, n (%)			0.0164
Refractory	30 (59)	27 (84)	
Intolerance	21 (41)	5 (16)	

GCS, gemcitabine, cisplatin and S-1.

Next, the outcomes of second-line chemotherapy and BSC in first-line GCS treatment refractory and intolerance groups, respectively, were compared. There were no differences in patient background in the refractory and intolerance groups (Tables SI and SII). In patients refractory to first-line GCS treatment, the 6- and 12-month OS rates were 53.3 and 32.0%, respectively, following second-line chemotherapy, and 3.7 and 0.0%, respectively, in the BSC group (P<0.0001) (Fig. S2A). In patients with intolerance to first-line GCS treatment, the 6- and 12-month OS rates were 85.7 and 61.9%, respectively, following second-line chemotherapy, and 20.0 and 20.0%, respectively, in the BSC group, respectively (P=0.0011) (Fig. S2B).

Following second-line chemotherapy regimens, the 12- and 24-month OS rates were 87.5 and 50.0%, respectively, in the GCS group, 33.3 and 17.8%, respectively, in the GC group, 100.0 and 75.0%, respectively, in the GS group, 66.7 and 44.4%, respectively, in the GEM group, and 16.7 and 0.0%, respectively, in the S-1 group (Fig. 2B). The GCS and GS groups had significantly improved OS rates compared with the S-1 group (P=0.0069 and P=0.0069, respectively) (Fig. 2B). In addition, the 12- and 24-month OS rates were 59.3 and 36.2%, respectively, for the 27 patients in the multidrug chemotherapy group (combinations such as GCS, GC and GS), and 26.9 and 9.0%, respectively, for the 24 patients within the single-agent chemotherapy group (P=0.0191) (Fig. 2C).

Discussion

GC is the global standard for first-line chemotherapy in patients with advanced BTC. In Japan, GS is also considered an alternative first-line chemotherapy. Due to the results of the recent KHBO1401 clinical study, a new standard treatment using a triplet GCS regimen could represent a replacement therapy. However, the prognosis for patients with advanced BTC remains poor, with a median OS time of only 11-15 months (4-6). Therefore, it is critically important to establish effective second-line therapy options after first-line chemotherapy.

The present study is the first to assess the efficacy of second-line chemotherapy in patients with advanced BTC who received first-line GCS chemotherapy. The administration of second-line chemotherapies after GCS therapy has been shown to significantly improve OS compared with BSC. Previous studies have also suggested that 15-25% of patients with BTC may be eligible for second-line chemotherapy despite there being no established second-line treatments (4,12,13). In the present study, 51 out of 83 (61%) patients with BTC who were refractory or intolerant to first-line GCS treatment received second-line chemotherapy. Almost all patients (90%) with an ECOG PS performance status of 0 or 1 were selected for second-line chemotherapy. Therefore, second-line chemotherapy may be most effective in patients with a good ECOG PS score.

Fluoropyrimidine-based regimens are the most common second-line regimens after GEM-based first-line therapy. However, few therapeutics have been considered as second-line therapies to be combined with fluoropyrimidines, and thus, none are currently recommended. Although the recent ABC-06 study demonstrated that second-line treatment with FOLFOX after GC resulted in improved patient survival

Table II. Patient characteristics among second-line regimens.

Factors	GCS (n=8)	GC (n=15)	GS (n=4)	GEM (n=6)	S-1 (n=18)
Median age (range), years	69 (60-78)	67 (42-78)	67 (64-69)	67 (44-81)	67 (39-78)
Sex, n (%)					
Male	6 (75)	7 (47)	3 (75)	1 (17)	11 (61)
Female	2 (25)	8 (53)	1 (25)	5 (83)	7 (39)
ECOG performance status, n (%)					
0	4 (50)	5 (33)	4 (100)	2 (33)	5 (28)
1	4 (50)	8 (53)	0 (0)	4 (67)	10 (56)
2	0 (0)	2 (13)	0 (0)	0 (0)	2 (11)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)
Primary tumor site, n (%)					
Gall bladder	2 (25)	2 (13)	0 (0)	2 (33)	7 (39)
Extrahepatic bile duct	6 (75)	7 (47)	3 (75)	1 (17)	4 (22)
Intrahepatic bile duct	0 (0)	6 (40)	1 (25)	2 (33)	7 (39)
Ampullary	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)
Disease stage, n (%)					
Unresectable	7 (88)	11 (73)	1 (25)	3 (50)	13 (72)
Locally advanced	3 (38)	2 (13)	1 (25)	0 (0)	3 (17)
Metastatic	4 (50)	9 (60)	0 (0)	3 (50)	10 (56)
Recurrent	1 (13)	4 (27)	3 (75)	3 (50)	5 (28)
Median GCS duration (range), weeks	12 (0-26)	20 (4-50)	40 (24-63)	26 (17-84)	40 (2-55)
GCS duration ≥24 weeks, n (%)	1 (13)	6 (40)	4 (100)	4 (67)	10 (56)
Discontinuation of GCS, n (%)					
Refractory	4 (50)	7 (47)	0 (0)	4 (67)	15 (83)
Intolerance	4 (50)	8 (53)	4 (100)	2 (33)	3 (17)

GEM, gemcitabine; GC, GEM plus cisplatin; GCS, GC plus S-1; GS, GEM plus S-1; ECOG, Eastern Cooperative Oncology Group.

compared with ASC for advanced BTC, it is unclear whether a doublet regimen that included FOLFOX would be superior to fluoropyrimidine alone (7).

In the present study, there was no significant difference in survival between single and doublet drug regimens (Fig. S3). However, significantly improved OS was observed with doublet and triplet regimens compared with single drug regimens, suggesting that multidrug chemotherapy after GCS may be more effective than single-agent chemotherapy. A total of 8 patients received a triplet GCS regimen as second-line chemotherapy. Second-line chemotherapy regimens were based on clinician discretion and patient preference. Therefore, it is assumed that patients in good condition would have preferred triplet GCS as second-line chemotherapy. Second-line chemotherapy using the same regimen as the first-line chemotherapy might be considered a re-challenge chemotherapy. Re-challenge chemotherapy may be performed in clinical practice for patients with advanced BTC, as second-line regimens are limited. However, there are no studies about the efficacy of re-challenge chemotherapy for BTC. Therefore, the efficacy and safety of GCS re-challenge chemotherapy needs to be well evaluated in future studies.

S-1 is one of the most commonly used second-line chemotherapeutics. Several studies showed that S-1 second-line chemotherapy could be well tolerated by patients with advanced BTC after receiving first-line GEM or GC, but its efficacy was modest (14-16). Although S-1 seems to have some degree of antitumor activity in patients with GEM-refractory advanced BTC, S-1 single-agent chemotherapy may be insufficient to improve the prognosis (15,16). In the present study, the GS regimen had a high OS rate compared with other regimens; all patients who received GS had a PS of 0 and were intolerant to GCS. In addition, the total duration of the GCS treatment period was >24 weeks. Therefore, selection bias might affect OS. Furthermore, it may be difficult to compare the efficacy of each regimen accurately due to the small sample size. Expanded prospective studies are required to further explore the efficacy of these regimens.

Recently, the development of genomic sequencing in BTC has rapidly progressed, and favorable treatment effects of molecular targeting agents, such as isocitrate dehydrogenase-1 inhibitors and fibroblast growth factor receptor inhibitors, in BTC, have been reported (17-19). Furthermore, the development of immune checkpoint inhibitors is promising, and for tumors with high microsatellite instability, pembrolizumab can be administered for multiple cancer types in various organs, including BTC (20). With these new developments, progress continues to be made toward effective systemic therapies

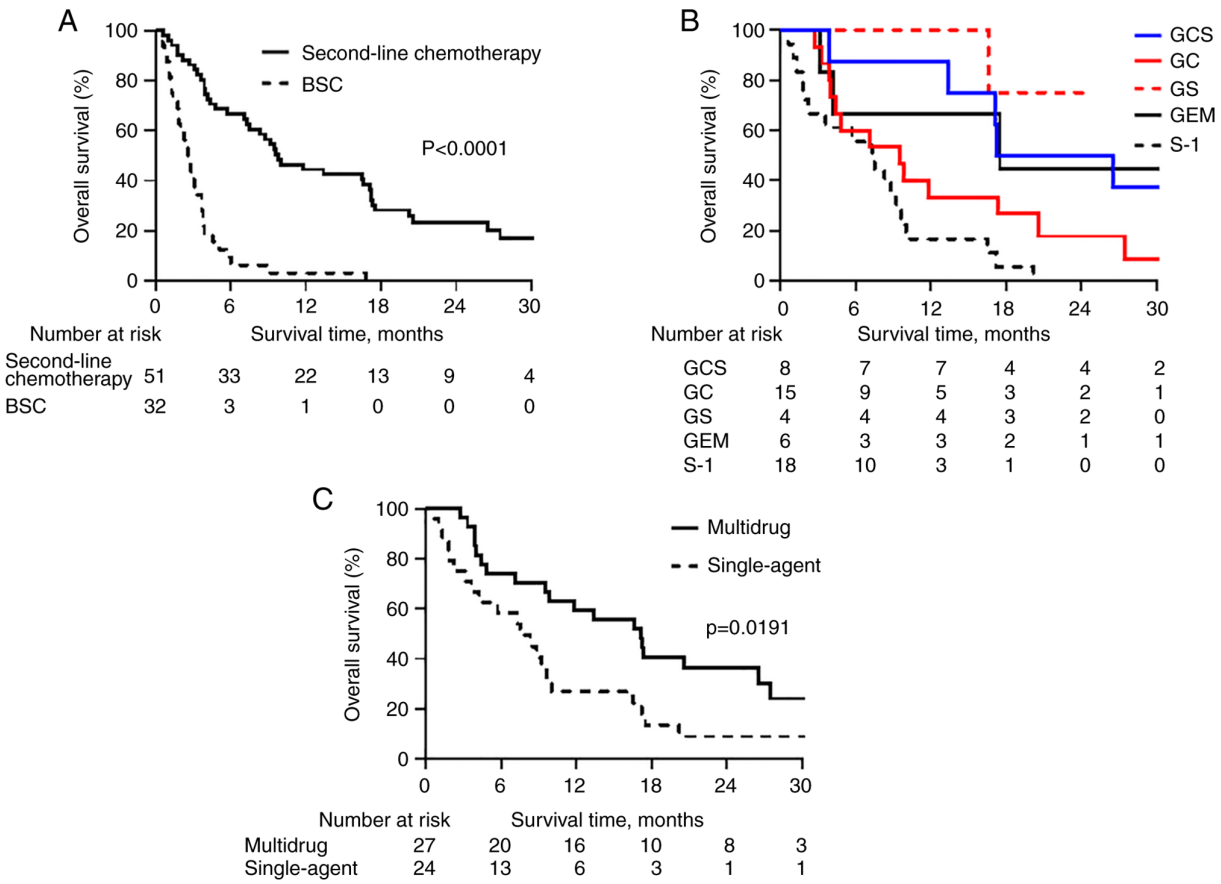

Figure 2. OS. (A) OS of patients who received second-line chemotherapy vs. BSC. (B) OS according to second-line chemotherapy regimens. (C) OS of patients who received multidrug chemotherapy vs. single-agent chemotherapy. OS, overall survival; BSC, best supportive care; GEM, gemcitabine; GC, GEM plus cisplatin; GCS, GC plus S-1; GS, GEM plus S-1.

for advanced BTC. However, there remain some issues to be resolved, such as the amount of time it takes for the results of genomic testing to be obtained, the lack of methods to obtain a sufficient sample volume in unresectable cases, the lack of effective therapeutic agents for genetic alterations and the cost of genomic testing (19,21-23).

The present exploratory study had several limitations. First, it included only Asian patients and non-randomized second-line chemotherapy regimens. Second, the number of patients treated with each regimen was small, so there was a potential selection bias for patients who received second-line chemotherapy. Finally, there were insufficient data to assess dose reduction, treatment interruption and toxicity profiles of the second-line chemotherapy regimens.

In conclusion, second-line chemotherapies could provide a new treatment option for patients with advanced BTC who become refractory or intolerant to first-line GCS therapy. In the present study, multidrug chemotherapy regimens tended to be more effective than single-agent regimens at improving patient survival. Prospective studies are needed to further explore the efficacy of second-line chemotherapy regimens in BTC.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

YS, HN and TI were responsible for the conception and design of the study. All the authors were involved in the study. All authors had full access to all the data reported in the study and had final responsibility for the decision to submit for publication. MK, SK, HW, DS, HE, HB, HK, TT, MU, MT, YN and EH collected and interpreted the data. YS, YN, KY and HN had full access to the raw data, analyzed the data and wrote the manuscript. TI and HN confirm the authenticity of all the raw data. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The study was initially approved by the Human Ethics Committee at Yamaguchi University (approval no. H30-199), and it was subsequently approved by the Institutional Review Boards of all participating centers(Osaka International Cancer Institute, Osaka; Osaka University Graduate School of Medicine, Osaka; Hokkaido University Graduate School of Medicine, Hokkaido; Wakayama Medical University, Wakayama; Kyoto University Hospital, Kyoto; Tohoku University Hospital, Miyagi; Kumamoto University, Kumamoto; Nihon University School of Medicine, Tokyo; Hyogo College of Medicine, Hyogo; Kindai University Faculty of Medicine, Osaka; Kobe University Hospital and Graduate School of Medicine, Hyogo; University of Tsukuba, Tsukuba; Fukushima Medical University, Aizu Medical Center, Fukushima; Saga University Hospital, Saga; Osaka City General Hospital, Osaka; Yokohama City University, Graduate School of Medicine, Yokohama; Toranomon Hospital, Tokyo; Osaka Rosai Hospital, Osaka; Kobe City Medical Center General Hospital, Kobe; Asahikawa Medical University, Hokkaido; Kansai Rosai Hospital, Hyogo; Tonan Hospital, Hokkaido; National Hospital Organization Osaka National Hospital, Osaka; Nagasaki University Hospital, Nagasaski; Toyonaka Municipal Hospital, Toyonaka; Kitano Hospital Medical Research Institute, Osaka). All participants provided written informed consent for participation in the study, which was conducted in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Matsukuma S, Tokumitsu Y, Shindo Y, Matsui H and Nagano H: Essential updates to the surgical treatment of biliary tract cancer. Ann Gastroenterol Surg 3: 378-389, 2019.
2. Matsuyama R, Yabusita Y, Homma Y, Kumamoto T and Endo I: Essential updates 2019/2020: Surgical treatment of gallbladder cancer. Ann Gastroenterol Surg 5: 152-161, 2021.
3. Sutherland M, Ahmed O, Zaidi A and Ahmed S: Current progress in systemic therapy for biliary tract cancers. J Hepatobiliary Pancreat Sci 29: 1094-1107, 2022.
4. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, *et al*: Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362: 1273-1281, 2010.
5. Morizane C, Okusaka T, Mizusawa J, Katayama H, Ueno M, Ikeda M, Ozaka M, Okano N, Sugimori K, Fukutomi A, *et al*: Combination gemcitabine plus S-1 versus gemcitabine plus cisplatin for advanced/recurrent biliary tract cancer: The FUGA-BT (JCOG1113) randomized phase III clinical trial. Ann Oncol 30: 1950-1958, 2019.
6. Ioka T, Kanai M, Kobayashi S, Sakai D, Eguchi H, Baba H, Seo S, Taketomi A, Takayama T, Yamaue H, *et al*: Randomized phase III study of gemcitabine, cisplatin plus S-1 versus gemcitabine, cisplatin for advanced biliary tract cancer (KHBO1401-MITSUBA). J Hepatobiliary Pancreat Sci: Jul 28, 2022 (Epub ahead of print).
7. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, Falk S, Gillmore R, Wadsley J, Patel K, *et al*: Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): A phase 3, open-label, randomised, controlled trial. Lancet Oncol 22: 690-701, 2021.
8. Zheng Y, Tu X, Zhao P, Jiang W, Liu L, Tong Z, Zhang H, Yan C, Fang W and Wang W: A randomised phase II study of second-line XELIRI regimen versus irinotecan monotherapy in advanced biliary tract cancer patients progressed on gemcitabine and cisplatin. Br J Cancer 119: 291-295, 2018.
9. Ying J and Chen J: Combination versus mono-therapy as salvage treatment for advanced biliary tract cancer: A comprehensive meta-analysis of published data. Crit Rev Oncol Hematol 139: 134-142, 2019.
10. Demols A, Borbath I, Van den Eynde M, Houbiers G, Peeters M, Marechal R, Delaunoit T, Goemine JC, Laurent S, Holbrechts S, *et al*: Regorafenib after failure of gemcitabine and platinum-based chemotherapy for locally advanced/metastatic biliary tumors: REACHIN, a randomized, double-blind, phase II trial. Ann Oncol 31: 1169-1177, 2020.
11. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET and Carbone PP: Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol 5: 649-655, 1982.
12. Bridgewater J, Palmer D, Cunningham D, Iveson T, Gillmore R, Waters J, Harrison M, Wasan H, Corrie P and Valle J: Outcome of second-line chemotherapy for biliary tract cancer. Eur J Cancer 49: 1511, 2013.
13. Walter T, Horgan AM, McNamara M, McKeever L, Min T, Hedley D, Serra S, Krzyzanowska MK, Chen E, Mackay H, *et al*: Feasibility and benefits of second-line chemotherapy in advanced biliary tract cancer: A large retrospective study. Eur J Cancer 49: 329-335, 2013.
14. Kobayashi S, Ueno M, Ohkawa S, Andou T, Kameda R, Yamamoto N and Morinaga S: A retrospective study of S-1 monotherapy as second-line treatment for patients with advanced biliary tract cancer. Jpn J Clin Oncol 42: 800-806, 2012.
15. Suzuki E, Ikeda M, Okusaka T, Nakamori S, Ohkawa S, Nagakawa T, Boku N, Yanagimoto H, Sato T and Furuse J: A multicenter phase II study of S-1 for gemcitabine-refractory biliary tract cancer. Cancer Chemother Pharmacol 71: 1141-1146, 2013.
16. Inoue H, Todaka A, Yamazaki K, Fushiki K, Shirasu H, Kawakami T, Tsushima T, Hamauchi S, Yokota T, Machida N, *et al*: Efficacy and safety of S-1 following gemcitabine with cisplatin for advanced biliary tract cancer. Invest New Drugs 39: 1399-1404, 2021.
17. Abou-Alfa GK, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad MJ, Gallinson D, Murphy AG, *et al*: Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: A multicentre, open-label, phase 2 study. Lancet Oncol 21: 671-684, 2020.
18. Abou-Alfa GK, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DV, Borad MJ, Bridgewater J, *et al*: Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): A multicentre, randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 21: 796-807, 2020.
19. Wakai T, Nagahashi M, Shimada Y, Prasoon P and Sakata J: Genetic analysis in the clinical management of biliary tract cancer. Ann Gastroenterol Surg 4: 316-323, 2020.

20. Marabelle A, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, *et al*: Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: Results from the phase II KEYNOTE-158 Study. J Clin Oncol 38: 1-10, 2020.
21. Ewalt MD, West H and Aisner DL: Next generation sequencing-testing multiple genetic markers at once. JAMA Oncol 5: 1076, 2019.
22. Arrichiello G, Nacca V, Paragliola F and Giunta EF: Liquid biopsy in biliary tract cancer from blood and bile samples: Current knowledge and future perspectives. Explor Target Antitumor Ther 3: 362-374, 2022.
23. Normanno N, Martinelli E, Melisi D, Pinto C, Rimassa L, Santini D and Scarpa A: Role of molecular genetics in the clinical management of cholangiocarcinoma. ESMO Open 7: 100505, 2022.