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Durvalumab-combined chemotherapy for biliary tract cancer in a Japanese expert center: initial 50 cases in daily practice

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ABSTRACT

Combination regimen consisting of gemcitabine, cisplatin, and durvalumab (GCD) has been employed for unresectable biliary tract cancer (BTC) since the end of 2022 in Japan. Here, we summarize our experience with GCD to demonstrate the clinical outcomes in a practical setting. Patients who underwent GCD for unresectable/recurrent BTC between January and December 2023 were investigated retrospectively. Data for maximal response rate (RR), disease control rate (DCR), and adverse events (AEs) were collected. Progression-free survival (PFS) and overall survival (OS) curves were generated using the Kaplan-Meyer method. Fifty (initially unresectable, n = 32; recurrence after surgery, n = 18) consecutive patients were enrolled, 19 of whom started GCD as second-line therapy or later. Overall RR was 24.0% including complete response in 1 (2%) patient and partial response in 11 (22%) patients; DCR was 68.0%. The median PFS and OS were 7.1 months and not reached, respectively. During a median follow-up period of 8.5 months, 8 (16%) patients underwent surgical resection. A total of 36 (72%) patients suffered Grade 3–5 AE, and 3 immune-related AE were controlled with injection of corticosteroid or observation. The efficacy of GCD for unresectable/recurrent BTC was confirmed in the practical setting, with acceptable toxicity, prolonged survival, and potential probability of resection.

Keywords: biliary tract cancer, durvalumab, prognosis, unresectable, immune related adverse event

Abbreviations:
AE: adverse event
BTC: biliary tract cancer
DCR: disease control rate
GCD: gemcitabine, cisplatin, and durvalumab
GCS: gemcitabine, cisplatin and S-1
OS: overall survival

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PFS: progression-free survival
RR: response rate

INTRODUCTION

Biliary tract cancer (BTC), which develops from any site within the entire biliary system, shows dismal prognosis[1,2] due to its aggressive biology, advanced nature at initial presentation, and the availability of few therapeutic options. Patients with resectable BTC generally undergo definitive surgical resection as the first-line approach, provided the surgical risk is acceptable. However, those with unresectable disease, those unsuitable for surgery, and those with disease relapse after surgery have no choice but to receive systemic therapy.[3] Although several multi-drug regimens are promising,[4-6] gemcitabine and cisplatin (GC) has remained the standard chemotherapy since around 2010.[7,8] This doublet therapy has provided a survival benefit to the types of patients described above, and the possibility of conversion surgery for a highly selected population. However, as is often the case with cytocidal chemotherapy, long-term survivorship is exceptionally low: nearly 0% at 2 to 3 years after initiation of GC regimen.[4,7]

Durvalumab is an immune checkpoint inhibitor that blocks PD-L1,[9] and it has been widely used in lung cancer.[10] In 2022, the TOPAZ-1 trial, a phase 3 randomized control study comparing a GC and durvalumab (GCD) regimen with GC, showed a significantly longer survival time for GCD compared with GC, with comparable toxicity.[11] Notably, a tail plateau phenomenon, with an overall survival (OS) rate of 25% at 2 years, was observed in the GCD group. Subsequently, at the end of 2022, the Japanese insurance system allowed this new triplet regimen only in the setting of unresectable and recurrent BTC. As experience with GCD is still limited, partly as a result of rare disease prevalence, efficacy and toxicity in the practical setting remain poorly understood.

We previously reported our clinical outcomes for GC for advanced BTCs[8] in a Japanese tertiary biliary center.[12-16] Here, we aimed to investigate the short-term outcomes of GCD on the basis of our early experience.

METHODS

Patients

Among patients with BTC who visited Nagoya University Hospital between January to December 2023, those who received GCD were reviewed retrospectively. The eligibility criteria were unresectable or recurrent BCT, an Eastern Cooperative Oncology Group (ECOG) performance status 0–2, neutrophil count ≥1,000/mL, and platelet count ≥100,000/mL. Patients with obstructive jaundice received biliary drainage to decrease total bilirubin to ≤3 mg/dL. The data regarding clinical background, treatment details, efficacy, toxicity, and prognosis were collected. The Institutional Review Board of Nagoya University approved the present study protocol (number: 2023-0023), and written informed consent for clinical data use was obtained from all patients included in this study.

GCD treatment

GCD consisted of intravenous administration of durvalumab with GC on a 21-day cycle for up to 8 cycles. Gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) were administered on days

1 and 8 of each cycle; durvalumab (1500 mg) was given on day 1 of each cycle. To prevent chemotherapy-induced nausea and vomiting, a 5-hydroxytryptamine 3 receptor antagonist and corticosteroid were routinely used. The chemotherapeutic agents, antiemetics and hydration were unified as an institutional protocol. If the neutrophil count was <1,000/mL or the platelet count was <100,000/mL, the schedule was postponed by one week.[8] When the former decreased to <500/mL, granulocyte colony-stimulating factor was administered. After completion of 8 cycles, durvalumab 1500 mg monotherapy was continued once every 4 weeks until disease progression or toxic intolerability, following the protocol of the TOPAZ-1 trial.[11]

Evaluation of efficacy and safety

Regarding follow-up, patients underwent computed tomography every 2–3 months, tumor marker examination every month, and physical examination and blood testing at every consultation. Treatment response was radiologically assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[17] and overall response rate (RR), and disease control rate (DCR) were calculated on the basis of the best response during the treatment period. OS was defined as the time between initiation of GCD and death from any cause or the last follow-up; progression-free survival (PFS) was defined as time between initiation of GCD to death from any cause, disease progression, or the last follow-up otherwise. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0).[18]

Statistical analysis

Continuous variables were shown as a median with range, and categorical variables were given as a number with percentage, unless otherwise specified. These were analyzed using Wilcoxon test and the chi-square test or Fisher's exact test, respectively. The status of all patients was surveyed on March 2024 and no patient was lost to follow-up. The associations of the chemotherapy regimen and other histopathological factors with PFS and OS were evaluated using the log-rank test. $P < 0.05$ was considered statistically significant. Statistical calculations were performed using JMP Pro software program, version 16 (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

The study included 50 patients (Table 1); 36 patients received GCD in Nagoya University Hospital and the remaining 14 patients received GCD in other hospitals. The most common tumor location was the gallbladder (n = 19, 38%), followed by the perihilar bile duct (n = 15, 30%), intrahepatic bile duct (n = 9, 18%), distal bile duct (n = 5, 10%), and the ampulla of Vater (n = 2, 4%). Fifteen (30%) patients had distant metastatic disease, 17 (34%) patients had locally advanced disease, and 18 (36%) patients had disease recurrence after surgery. Thirty-one patients underwent GCD as first-line therapy, whereas 19 patients underwent previous therapy, including GC (n = 16, 32%), GC and S-1 (GCS; n = 4, 8%), and gemcitabine and S-1 (n = 2, 4%) with some overlaps. During a median follow-up period of 8.5 months (range 4.0 to 14.1), GCD was given in 6 (range 1 to 13) cycles in median. Fourteen (28%) patients underwent durvalumab monotherapy following completion of 8 cycles of GCD. Causes for termination of GCD were tumor progression (n = 15, 30%), AE (n = 7, 14%) and conversion strategy to resection (n = 8, 16%). Seven of the 32 patients with initially unresectable disease and 1 of the 18 patients with postoperative disease relapse underwent surgical resection, providing an overall conversion

rate of 16% after GCD therapy. Among the 8 patients who received conversion surgery, two patients (25%) showed major pathological response including one patient (13%) of pathological complete response (CR), and four patients (50%) showed pathologically negative resection margin. Treatment after GCD failure included S-1 (n = 3, 6%), gemcitabine (n = 1, 2%), and best supportive care (n = 18, 36%; Table 2).

Table 1 Patient characteristics

Characteristics		n	(%)
Gender	Male	32	64
Age, years		68 (33–85)	
Performance status	0	46	92
	1	3	6
	2	1	2
Primary tumor site	Intrahepatic bile duct	9	18
	Perihilar bile duct	15	30
	Gallbladder	19	38
	Distal bile duct	5	10
	Ampulla of Vater	2	4
Disease status	Initially unresectable, distant metastasis	15	30
	Initially unresectable, locally advanced	17	34
	Postoperative recurrence	18	36
Previous chemotherapy*	Gemcitabine and cisplatin	16	32
	Gemcitabine, cisplatin and S-1	4	8
	Gemcitabine and S-1	2	4
	Pemigatinib	1	2

*There are some overlaps.

Table 2 Details of GCD treatment

Characteristics		n	(%)
Follow up period after GCD induction (months)	Median (range)	8.5 (4.0–14.1)	
GCD treatment cycles	Median (range)	6 (1–13)	
Transition to durvalumab monotherapy		14	28
Cause for termination of GCD	Progression	15	30
	Adverse event	7	14
	Conversion surgery	8	16
Treatment after GCD failure	S-1	3	6
	Gemcitabine	1	2
	Best supportive care	18	36

GCD: gemcitabine, cisplatin, and durvalumab

Efficacy

The best overall response is shown in Figure 1. There was one patient with CR (2%), 11 with partial response (PR; 22%), 22 with stable disease (SD; 44%) and 13 with progressive disease (PD; 26%); the remaining 3 patients had unmeasurable disease, treated as not evaluable (NE; 6%). Subsequently, overall RR was 24.0%, and DCR was 68.0% (Figure 1A). Limited to 31 patients with GCD as first-line therapy, CR, PR, SD, PD and NE were 1 (3%), 8 (26%), 16 (52%), 4 (13%) and 2 (6%), respectively, indicating a RR of 29.0% and DCR of 80.6%, respectively (Figure 1B). Nineteen patients who received later-line GCD exhibited a median PFS of 4.0 months, RR of 15.8%, and DCR of 47.4%, which were significantly worse than those in first-line GCD (P = 0.001). Limited to 29 patients with measurable disease among the 31, RR and DCR were 31.0% (9/29) and 86.2% (25/29), respectively. Median time to response was 2.3 (1.2–4.6) months.

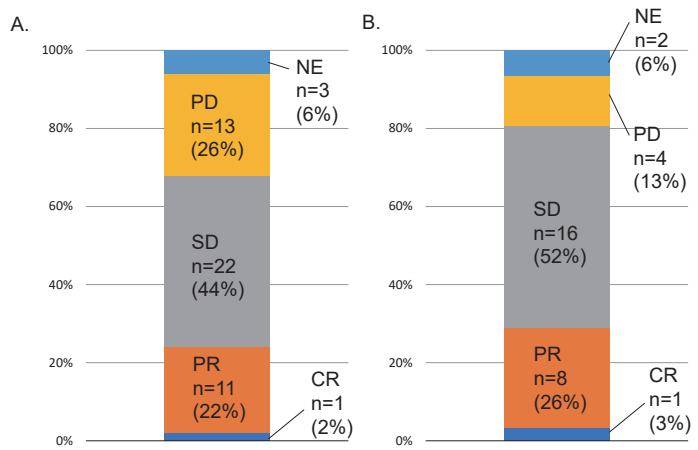

Fig. 1 Best overall response

Fig. 1A: Response rate of GCD in a total of 50 patients
Fig. 1B: Response rate in patients with GCD as first-line therapy (n = 31)
GCD: gemcitabine, cisplatin, and durvalumab
CR: complete response
PR: partial response
SD: stable disease
PD: progressive disease
NE: not evaluable

OS was 85.4% at 6 months, 70.2% at 9 months with a not-reached median, while PFS was 58.0% at 6 months and 37.2% at 9 months with a median of 7.1 months (Figure 2). Patients with initially unresectable disease and those with recurrent disease had comparable survival (Figure 3A, B). Patients with GCD as the first-line therapy (n = 31, 62%), (OS: 92.4% and 80.5%, PFS: 79.8% and 49.4% at 6 and 9 months, median PFS of 7.7 months) showed better survival than those with GCD as the second- or later-lines (n = 19, 38%), (OS: 73.7% and 54.6%, PFS: 26.3% and 19.7% at 6 and 9 months, median PFS of 4.0 months; Figure 3C, D). Twenty-seven (54%) patients who met the eligibility criteria for TOPAZ-1 protocol showed significantly better survival than 23 patients who did not (OS: 85.2% vs 54.0%, PFS: 52.8% and 20.3% at 9 months; Figure 4A, B).

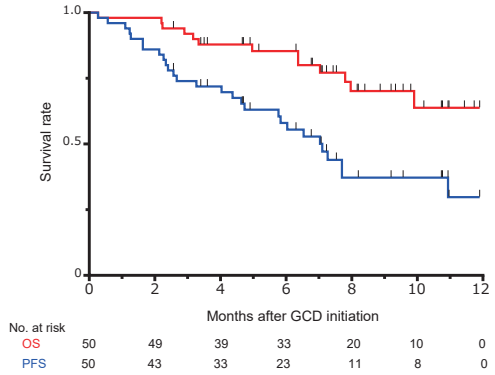

Fig. 2 Survival curves after GCD initiation
GCD: gemcitabine, cisplatin, and durvalumab
OS: overall survival
PFS: progression-free survival

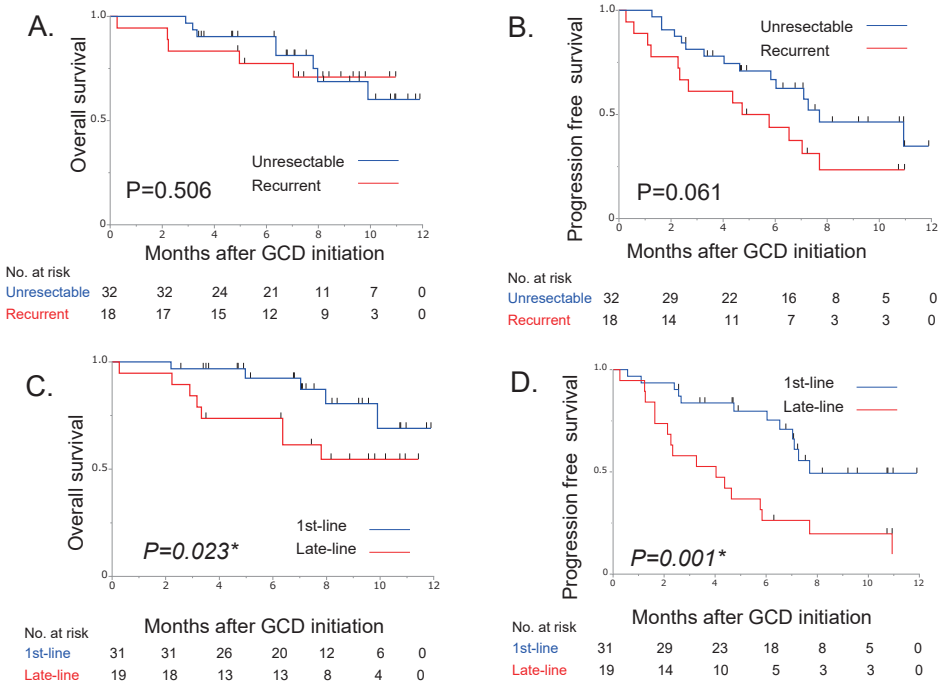

Fig. 3 Survival curves for comparison between the divided groups
Fig. 3A: Overall survival in unresectable cases (n = 32) and recurrent cases (n = 18)
Fig. 3B: Progression-free survival in unresectable cases (n = 32) and recurrent cases (n = 18)
Fig. 3C: Overall survival in patients with GCD as first-line treatment (n = 31) and late-line treatment (n = 19)
Fig. 3D: Progression-free survival in patients with GCD as first-line treatment (n = 31) and late-line treatment (n = 19)
GCD: gemcitabine, cisplatin, and durvalumab

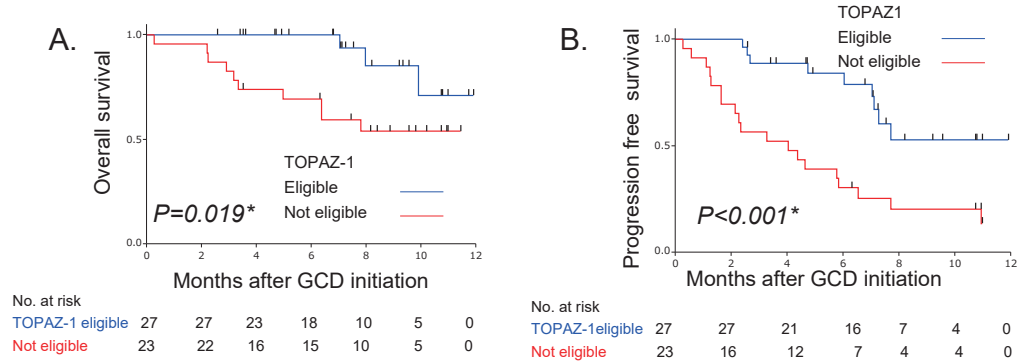

Fig. 4 Survival curves for comparison between TOPAZ-1 eligible and not eligible patients
Fig. 4A: Overall survival in TOPAZ-1 eligible (n = 27) and not eligible cases (n = 23)
Fig. 4B: Progression-free survival in TOPAZ-1 eligible (n = 27) and not eligible cases (n = 23)

AEs

Thirty-six of 50 patients (72%) had AEs of grade 3 and above (Table 3), reflecting a similar rate of AEs observed in the TOPAZ-1 trial, in which grade 3 or 4 AEs were 75.7% in the GCD group.[11] All AEs were controlled in the usual manner, except for a critical event of non-occlusive mesenteric ischemia, which caused death of the patient on day 8 after initiation of the first cycle of GCD as late-line therapy for recurrent disease after resection of the ampulla of Vater (mortality rate 2.0%). The mortality rate of the GCD group in the TOPAZ-1 trial was 3.6%.[11] Immune-related AE (irAE) were observed in 3 patients. A patient with grade 2 myocarditis after 3 cycles of GCD recovered without any treatment except for admission to our hospital and observation. The other patient with grade 4 hepatitis after 1 cycle of GCD required therapy

Table 3 Adverse events of grade 3 or above, and immune-related adverse events

	Number (%)
Hematological (Grade 3 or above)	
Neutropenia	20 (40%)
Anemia	9 (18%)
Thrombocytopenia	3 (6%)
Non-hemtological (Grade 3 or above)	
Fatigue	2 (4%)
Anorexia	1 (2%)
Hypercalcemia	1 (2%)
Joint pain	1 (2%)
Non-occlusive mesenteric ischemia	1 (2%)
Pleural effusion	1 (2%)
Pneumonitis	1 (2%)
Immune-related adverse events	
Myocarditis	1 (2%)
Hepatitis	1 (2%)
Nephritis	1 (2%)

with prednisolone which improved the liver enzymes. The third patient suffered grade 3 nephritis after 4 cycles of GCD, which was ameliorated only with termination of GCD treatment. The latter two patients had Grade 3 or 4 irAEs with an incidence of 4%.

DISCUSSION

Since the national insurance system in Japan approved the TOPAZ-1 regimen (ie, GCD) for unresectable BTC in December 2022,[11] the clinical experience with this new chemotherapy remains limited, due to the relatively rare disease nature of BTC. Therefore, we conducted a single-center, retrospective collective study in Japanese daily practice. Our cohort revealed that extrahepatic cholangiocarcinoma and gallbladder cancer formed a main target in Japan, and showed a comparable therapeutic effect of first-line GCD with acceptable toxicity. Grade 3–4 irAEs were a rare event (4%), although 2.4% in TOPAZ-1 study.[11] These findings suggest that the TOPAZ-1 regimen had reproducible efficacy in the setting of daily practice in Japan.

Although BTC is a broad disease entity including intrahepatic/extrahepatic cholangiocarcinoma and gallbladder cancer, all these types are treated similarly in the oncologic field due to the analogic derivation from the biliary epithelium or cholangiocyte. The prevalence and etiology of BTC significantly differs among geographic regions.[19] Intrahepatic cholangiocarcinoma is more common in Western countries and Thailand; however, extrahepatic cholangiocarcinoma is the most common in East Asia. Therefore, a global multicenter study in BTC oncology is required. In the TOPAZ-1 study, intrahepatic/extrahepatic cholangiocarcinoma and gallbladder cancer accounted for 55%, 19%, and 25%, respectively, and the prolonging effect of survival by GCD was inversely related to incidence. As we anticipated before initiation of a GCD regimen, the subtype proportion in our cohort (18%, 40%, and 38%) was drastically different from that in the TOPAZ-1 study.

Notably, first-line GCD showed a median PFS of 7.7 months, RR of 29.0%, and DCR of 80.6% in the present cohort, which is comparable to those in the TOPAZ-1 study where they were 7.2 months, 26.7% and 85.3%, respectively. In addition, another Italian study[20] evaluating GCD for advanced BTC (n = 145), in which intrahepatic cholangiocarcinoma accounted for 60% of cases, reported a median PFS of 8.9 months, RR of 34.5% and DCR of 87.6%. The overall therapeutic effect in a clinical study may increase with a higher proportion of intrahepatic cholangiocarcinoma in the study sample. In addition, non-intrahepatic tumor was likely to exhibit infiltrating or wall-thick morphology, which is difficult to measure. This could explain a minute inferiority in our cohort with non-intrahepatic cholangiocarcinoma of as high as 78%. Nonetheless, the present study demonstrated a reproducible and reliable benefit of GCD therapy, independent of geographical region, ethnicity, and tumor type.

The present study included 19 patients who received GCD as second or later-line therapy, 16 of which changed regimen from GC to GCD after January 2023. The effect was a median PFS of 4.0 months, RR of 15.8%, and DCR of 47.4%, which was obviously inferior to those in the present first-line GCD or TOPAZ-1 study. Now that there is a limited available chemotherapy against BTC in Japan, second-line GCD could be considered in patients failing first-line therapy. Further studies will be needed to confirm the effect of later-line GCD, because the present sample was too limited. Another finding was that definitive resection was performed in 8 patients with initially unresectable disease or postoperative disease relapse, giving an overall conversion rate of 16%. In contrast, TOPAZ-1 included only 3 (0.9%) patients who received resection after GCD chemotherapy. The difference in conversion rate should be carefully interpreted because of heterogeneous disease nature and different surgical indications. The present 16% may be unreliable due to referral bias associated with the tertiary function of our institution. Major

pathological RR of 25% (2/8) in the present GCD cohort seemed better than previous report by Noji et al[21] about conversion surgery after other regimens without immune-checkpoint inhibitor (4/24, 17%). Meanwhile, the R0 rate of 50% (4/8) in the present study was worse than 83% (20/24) by Noji et al. Simple comparison is inappropriate because of very limited sample size and different surgical indication. Nonetheless, converting unresectable cases to resectable ones by immunochemotherapy is promising for providing a chance of long-term survival.[21,22]

The national health insurance in Japan allows oral S-1 chemotherapy for a wide range of cancers including gastric, colorectal, pancreatic, and biliary cancers. In this regional situation, another triplet chemotherapy including GCS has been used for BTC in Japan according to the MITSUBA trial,[6] which revealed a median OS of 13.5 months, median PFS of 7.4 months and 41.5% of RR by the GCS, with comparable AEs to GC. As these results were similar to those in TOPAZ-1, GCS has been another option in addition to GCD for advanced BTC in Japan. Most surgeons have an interest in GCS due to its high tumor response of 41.5%, expecting conversion surgery. Nakamura et al reported that 6 patients underwent resection among 119 patients allocated to the GCS group, giving a conversion rate of 5.0% in the MITSUBA study.[23] Interestingly, these 6 patients initially had metastatic disease rather than locally advanced disease. Therefore, conversion surgery for locally advanced tumors remains challenging. Currently, a phase III trial comparing GCS and GCD in initially unresectable BTC (YOTSUBA trial) is ongoing in Japan, and this study will make a conclusion regarding the preferred first-line approach in Japan.[24]

The present study had several limitations. First, patient number is limited as this was a single-center study with a one-year collection period. Relatively rare disease was also an attributable factor. Second, the present single-arm setting may be difficult to prove the scientific efficacy of the regimen. Finally, our cohort was characterized by heterogeneous background, which made it difficult to evaluate the outcomes definitively. Nonetheless, the present study demonstrated a similar outcome to TOPAZ-1, a global large-scale study, even in Japanese daily practice with different tumor locations for BTC.

In conclusion, we reported the outcomes from early experiences using the GCD regimen for BTC, and the present results showed reproducibility and feasibility in a real-world practice setting.

CONFLICT OF INTEREST

TE has received personal fees from Taiho Pharmaceutical and AstraZeneca. The other authors declare that they have no competing interest.

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