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Comparison of monotherapy and combination therapy for older patients with advanced biliary tract cancer: a retrospective study

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Abstract

Background The current standard first-line treatment for patients with advanced biliary tract cancer (BTC) is a combination chemotherapy regimen. However, whether the efficacy of combination therapy is superior to that of monotherapy in older patients with BTC remains unclear. Therefore, in this study, we aimed to compare the efficacy and safety of monotherapy with those of combination therapy in such patients.

Methods We retrospectively enrolled 157 patients with unresectable or recurrent BTC aged ≥ 75 years who received systemic chemotherapy between August 2011 and November 2020. We compared the efficacy and safety of combination therapy (gemcitabine [GEM] + cisplatin and GEM + S-1) with those of monotherapy (GEM or S-1 alone). We assessed patients' characteristics, survival, adverse events, and dose intensity. Statistical significance was set at $p < 0.05$.

Results Patients who received monotherapy were older and had worse performance status (PS), lower albumin levels, and higher carcinoembryonic antigen (CEA) levels than those who received combination therapy. The median overall survival (OS) was 16.4 and 12.8 months in the combination therapy and monotherapy groups, respectively (Hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.47–1.01), with a trend towards longer OS observed with combination therapy. However, multivariable analysis did not show superior OS with combination therapy (HR, 1.05; 95% CI, 0.66–1.68). Multivariable analysis also revealed gallbladder cancer, CEA, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) levels as prognostic factors for OS. Regarding safety, the incidence of grade ≥ 3 adverse events was significantly higher in the combination therapy group than in the monotherapy group (79% vs. 53%, $p = 0.001$); however, the rate of treatment discontinuation was approximately 10% in both groups, with no treatment-related deaths, suggesting that toxicities are manageable even in older patients.

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Conclusions Combination therapy is not necessarily recommended for older patients with BTC. Selecting an appropriate chemotherapy regimen based on an individual's condition is important.

Keywords Geriatrics, Gemcitabine, Cisplatin, S-1, Biliary tract cancer, Monotherapy, Combination therapy, Systemic chemotherapy, And prognosis

Background

Malignant biliary tract cancer (BTC) originates from the epithelium of the biliary system [1, 2]. BTC manifests as cancer of the gallbladder, intrahepatic bile duct, extrahepatic bile duct, or ampulla of Vater [3, 4]. In Japan, 65.7% of patients with BTC are aged > 75 years, and this proportion is increasing [5], with most diagnosed at an advanced stage and often experiencing cancer recurrence even after radical surgery [6, 7]. BTC is one of the cancers with the worst prognosis [8]. Systemic chemotherapy is usually indicated for patients with advanced BTC, defined as an initially unresectable or recurrent disease after surgery [9, 10].

Currently, the standard first-line treatment regimen for patients with advanced BTC is gemcitabine (GEM) plus cisplatin (GC) combination chemotherapy, based on the results of the ABC-02 phase III trial [11]. S-1 is an oral fluoropyrimidine agent consisting of tegafur (a prodrug of 5-fluorouracil [5-FU]) and the 5-FU modulators, "gimeracil and oteracil." In a recent randomized phase III trial (FUGA-BT/JCOG1113), GEM plus S-1 (GS) combination therapy was reported to be non-inferior to GC combination therapy in patients with advanced BTC [12]. Therefore, the guideline for BTC treatment in Japan recommends GC or GS as the first-line chemotherapy. However, the patients enrolled in these trials were much younger than those in actual clinical practice. The median age of patients in the ABC-02 and FUGA-BT trials was 63 and 67 years, respectively. Notably, the enrollment of a small number of older patients in oncology clinical trials has been a long-term issue [13]. Older patients are more likely to experience higher toxicity owing to age-related physical decline and multiple comorbidities [14]. Therefore, the efficacy and safety of chemotherapy in older patients is unclear. Furthermore, whether the efficacy of GEM plus S-1 combination therapy is superior to that of GEM or S-1 monotherapy in older patients remains unclear. With the global population aging, the number of patients with BTC is increasing [15], indicating the increasing need to evaluate the outcome of systemic chemotherapy in older patients with advanced BTC. Therefore, in this study, we aimed to compare the efficacy and safety of monotherapy with those of combination therapy in patients with advanced BTC aged ≥ 75 years.

Methods

Patients

In this single-center retrospective study, we enrolled 157 consecutive patients with unresectable or recurrent BTC aged ≥ 75 years who received GC, GS, GEM, or S-1 as first-line treatment at the Kanagawa Cancer Center, Japan, between August 2011 and November 2020. Patients with histologically or cytologically confirmed BTC were eligible for the study. The study was conducted in compliance with the standards of the Declaration of Helsinki and current ethical guidelines and approved by the Institutional Review Board of the Kanagawa Cancer Center. Written informed consent was obtained from all patients before receiving systemic chemotherapy. In addition, the participants were given the opportunity to opt out of having their information published.

Treatment

The GC combination therapy comprised GEM (1000 mg/m^2) and cisplatin (25 mg/m^2), administered through infusion on days 1 and 8. This regimen was repeated every 3 weeks. Cisplatin treatment was continued for up to 16 times (400 mg/m^2 in total). After cisplatin treatment was discontinued due to a cumulative dose, patients received GEM monotherapy (1000 mg/m^2 of GEM) through infusion on days 1, 8, and 15. This regimen was repeated every 4 weeks. The GS combination therapy comprised GEM (1000 mg/m^2) administered through infusion on days 1 and 8 and oral S-1 administered at a dose based on the body surface area (BSA) (60 mg/day for a BSA < 1.25 m^2, 80 mg/day for a BSA between 1.25 and 1.50 m^2, and 100 mg/day for a BSA > 1.50 m^2) twice daily on days 1–14. This regimen was repeated every 3 weeks. S-1 monotherapy comprised oral S-1 administered twice daily on days 1–28 at a dose based on the BSA (80 mg/day for a BSA < 1.25 m^2, 100 mg/day for a BSA between 1.25 and 1.50 m^2, and 120 mg/day for a BSA > 1.50 m^2). This regimen was repeated every 6 weeks. The treatment regimen and initial dose were determined by the attending physician according to the patient's preference and general condition.

Computed tomography was performed every 6–8 weeks using contrast media, if possible. The radiological response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (version 1.1) [16]. We continued administering the first-line treatment until disease progression, intolerable adverse events, or patient refusal. Disease progression

was diagnosed based on radiological and clinical findings. The second-line treatment was administered based on the patient's general condition, and the regimen was selected according to the approval condition in Japan.

Efficacy and safety evaluation

We evaluated patients' overall survival (OS), progression-free survival (PFS), adverse events, and dose intensity (DI). OS was defined as the time from the first day of treatment to the date of death due to any reason. Patients who were alive were censored at the last follow-up visit. PFS was defined as the time from the first day of treatment to the date of confirmed progressive disease (PD) or death due to any reason. Patients without disease progression who were alive at the time of data cutoff were censored. For safety evaluation, adverse events during treatment were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) [17]. DI was defined as the administered dose of the agent divided by the unit time (weeks).

Statistical analysis

We compared the efficacy and safety of combination therapy (GC and GS) with those of monotherapy (GEM and S-1). Continuous variables were presented as medians with their ranges and compared using the Wilcoxon rank-sum test or *t*-test, if applicable. Categorical variables were presented as counts with percentages and compared using Fisher's exact test. When the continuous values were divided into two groups, the reference value was used as the cutoff value. The median OS and PFS were calculated using the Kaplan–Meier method. When comparing the OS and PFS between the two groups, the *p*-value was calculated using the unstratified log-rank test. Statistical significance was set at $p < 0.05$. A Cox proportional hazards model was used to estimate the hazard ratio (HR) and its 95% confidence interval (CI). Multivariable analysis was performed on OS to examine the prognostic factors. All statistical analyses were performed using JMP PRO (version 15.0.0; SAS Institute, Inc.). The clinical data cutoff was performed on September 19, 2021.

Results

Patients

Among the 157 included patients, 50 (31.8%) were aged > 80 years. Table 1 presents patients' characteristics. The median age of the patients in the combination therapy and monotherapy groups was 78 (range: 75–86) and 81 (range: 75–90) years, respectively ($p < 0.001$). The number of patients with the Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, 1, and 2 was 73 (73%), 23 (25%), and 2 (2%), respectively, in the combination therapy group and 32 (56%), 17 (30%), and

Table 1 Patients' characteristics

	Combination therapy (*N* = 100)		Monotherapy (*N* = 57)		*p*-value
Age, years, median (range)	78	(75–86)	81	(75–90)	< 0.001†
Sex, Female, n (%)	33	(33)	21	(37)	0.626‡
BMI (kg/m^2), median (range)	21.9	(14.1–35.7)	21.4	(13.4–28.8)	0.18‡
ECOG PS, n (%)	73	(73)	32	(56)	0.007‡
0	25	(25)	17	(30)	
1	2	(2)	8	(14)	
2					
Primary tumor sites, n (%)	8	(8)	2	(4)	0.503‡
Ampulla	23	(23)	18	(32)	
Gallbladder	26	(26)	14	(25)	
Intrahepatic bile duct	43	(43)	23	(39)	
Extrahepatic bile duct					
Disease stage, n (%)	84	(84)	47	(82)	0.062‡
Unresectable	16	(16)	10	(18)	
Recurrence					
NLR, median (range)	2.46	(0.86–23.6)	2.82	(0.75–21.7)	0.32†
Albumin (g/dL), median (range)	3.6	(2.0–4.4)	3.4	(2.2–4.7)	0.005†
CRP (mg/dL), median (range)	0.53	(0.03–9.53)	0.95	(0.02–11.28)	0.226†
CEA (ng/mL), median (range)	3.0	(0.9–588.3)	4.6	(1.0–418)	0.033†
CA 19 – 9 (U/mL), median (range)	96.3	(2–1126400)	4337	(2–1628200)	0.366†
Biliary drainage, n (%)	55	(55)	30	(53)	0.774‡
Second-line chemotherapy, n (%)	55	(55)	24	(42)	0.119‡

BMI, body-mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA 19 – 9, carbohydrate antigen 19 – 9

†Student *t*-test, ‡Fisher's exact test

8 (14%), respectively, in the monotherapy group, with significant differences observed between the two groups ($p = 0.007$). Serum albumin and carcinoembryonic antigen (CEA) levels also differed between the combination therapy and monotherapy groups (median albumin level: 3.6 g/dL vs. 3.4 g/dL, $p = 0.005$; median CEA level: 3.0 ng/mL vs. 4.6 ng/mL, $p = 0.033$). Patient's backgrounds in the patients who received GC combination and GEM monotherapy were comparable with those of all the combination regimen and monotherapy groups, respectively (Supplement Table 1).

Treatment

A total of 100 patients (63.7%) received combination therapy, whereas 57 patients (36.3%) received monotherapy. In the combination therapy group, 92 patients received GC and eight received GS, while in the monotherapy group, 50 patients received GEM and seven received S-1. The initial doses of the combination therapy and monotherapy were reduced in seven (7%) and eight (14%) patients, respectively. In the combination therapy group, the median DIs of GEM and cisplatin in the GC regimen were 516.3 and 10.9 mg/m^2/week, respectively, whereas those of GEM and S-1 in the GS regimen were 603.7 and 336.2 mg/m^2/week, respectively. In the monotherapy group, the median DIs of GEM and S-1 were 619.3 and 648.8 mg/m^2/week, respectively.

Treatment was discontinued due to disease progression, adverse events, and other reasons in 83 (83%), 10 (10%), and seven (7%) patients, respectively, in the combination therapy group and 44 (77%), five (9%), and eight (14%) patients, respectively, in the monotherapy group. The distribution of the reasons for treatment discontinuation did not differ between the two groups ($p = 0.37$).

Survival

The median OS was 16.4 (95% CI, 13.7–20.1) and 12.8 (95% CI, 7.5–15.7) months in the combination therapy and monotherapy groups, respectively (HR, 0.69; 95% CI, 0.47–1.01; $p = 0.06$) (Fig. 1). The median PFS was 9.2 (95% CI, 6.7–11.3) and 5.7 (95% CI, 4.9–8.6) months in the combination therapy and monotherapy groups, respectively (HR, 0.79; 95% CI, 0.56–1.12; $p = 0.19$) (Fig. 2). Notably, although the differences in OS and PFS were not significant, patients' backgrounds differed between the two groups; therefore, the influence of patients'

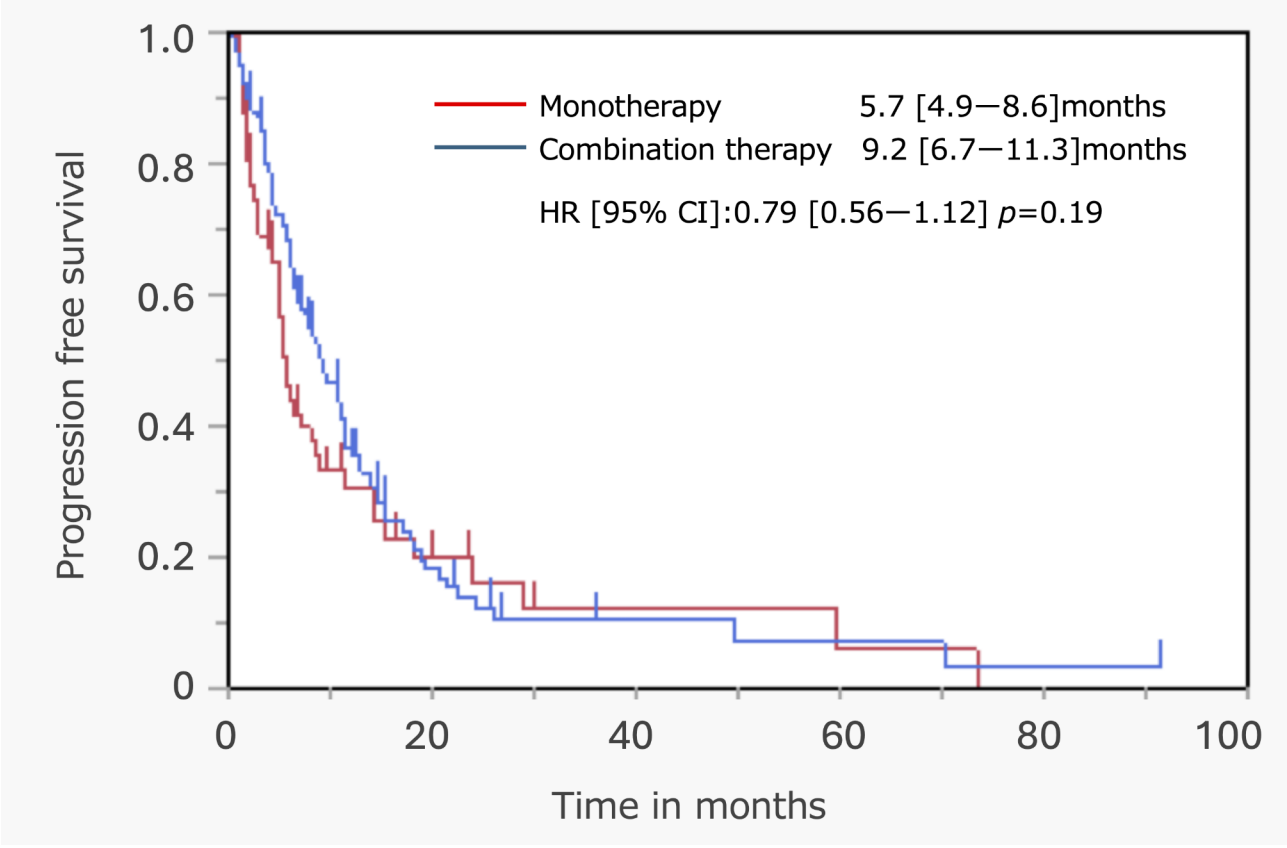

Fig. 1 Overall survival stratified by treatment group. Kaplan–Meier curves for overall survival in the combination therapy group versus the monotherapy group. The median overall survival in the combination therapy and monotherapy groups was 16.4 (95% CI, 13.7–20.1) and 12.8 (95% CI, 7.5–15.7) months, respectively. CI, confidence interval; HR, hazard ratio

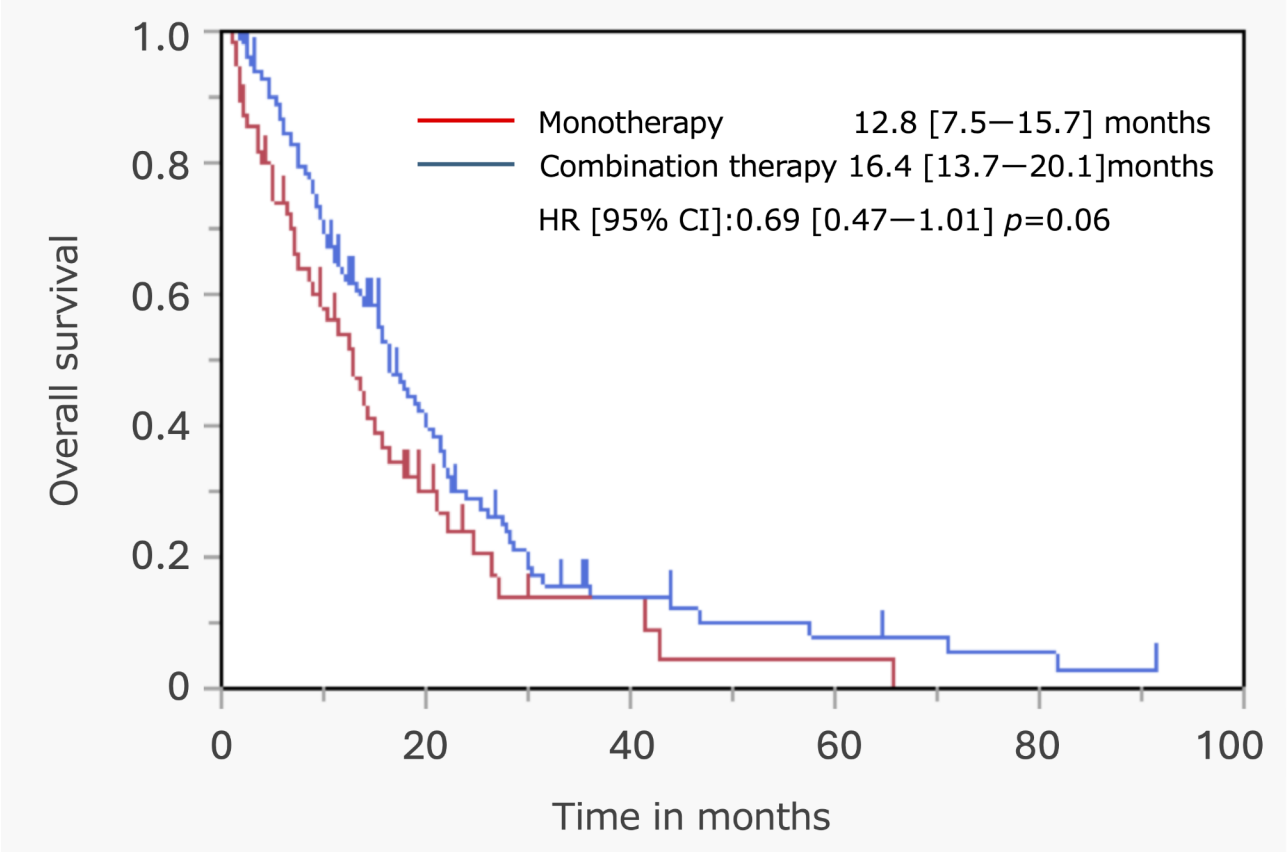

Fig. 2 Progression-free survival stratified by treatment group. Kaplan–Meier curves for overall survival in the combination therapy group versus the monotherapy group. The median progression-free survival in the combination therapy and monotherapy groups was 9.2 (95% CI, 6.7–11.3) and 5.7 (95% CI, 4.9–8.6) months, respectively. CI, confidence interval; HR, hazard ratio

backgrounds should be considered. Multivariable analysis revealed that combination therapy did not result in an OS superior to that of monotherapy (HR, 1.08; 95% CI, 0.69–1.73) (Table 2). The analyses of the patients who received GC combination and GEM monotherapy showed comparable results of the entire cohort (Supplement Table 2).

Subgroup analysis showed a trend towards prolonged OS with combination therapy compared to that with monotherapy in patients aged < 80 years, those with a body mass index (BMI) ≥ 22 kg/m^2, and those with an ECOG PS of 0. A Supplement figure shows this in more detail [see Supplement Fig. 1]. The HR for combination therapy (vs. monotherapy) was 0.57 (95% CI, 0.33–0.98), 0.41 (95% CI, 0.23–0.70), and 0.64 (95% CI, 0.40–1.03), respectively.

Radiological response

The objective response rates in the combination and monotherapy groups were 9.0% and 3.5% ($p = 0.17$), respectively, whereas the disease control rates were 89.0% and 78.9% ($p = 0.09$), respectively.

Safety

Table 3 presents the incidence of grade ≥ 3 adverse events. The prevalence of grade ≥ 3 hematological adverse events was higher in the combination therapy group (70%) than in the monotherapy group (44%) ($p = 0.002$). The trend was particularly significant in cases of neutropenia (77%). Regarding grade ≥ 3 non-hematological adverse events, there was a trend toward more adverse events in the combination therapy group (23%), although no significant differences were observed between the two groups ($p = 0.214$). The prevalence of anorexia (5.3%) and sepsis (5.3%) was higher in the monotherapy group, whereas that of skin rash (5%) and interstitial pneumonia (3%) was higher in the combination therapy group. There were no treatment-related deaths in this study.

Discussion

This single-center retrospective study was conducted to compare the efficacy and safety of standard combination therapies with those of monotherapies in older patients with unresectable BTC. In the present study, older patients with low PS, low albumin levels, and high CEA levels were more frequently treated with monotherapy.

Table 2 Univariate and multivariable analyses of factors affecting overall survival

	Univariate			Multivariable		
	Hazard ratio	**95% CI**	***p*-Value**	**Hazard ratio**	**95% CI**	***p*-Value**
Baseline characteristics						
Age ≥ 80 years	1.33	0.90–1.97	0.152	1.33	0.84–2.12	0.219
Sex, Female	1.18	0.81–1.70	0.386			
BMI < 22 kg/m^2	1.04	0.73–1.49	0.808			
ECOG PS of 0	0.46	0.21–0.66	< 0.001	0.63	0.42–0.95	0.031
Tumor characteristics						
Primary tumor sites, Gallbladder	2.81	1.86–4.26	< 0.001	2.00	1.28–3.11	< 0.001
Recurrence	0.93	0.57–1.49	0.763			
Laboratory values						
NLR ≥ 2.6	1.63	1.15–2.33	0.007	1.76	1.18–2.61	0.005
Albumin < 3.5 g/dL	1.66	1.16–2.36	0.005	1.28	0.84–1.95	0.249
CRP ≥ 1.0 mg/dL	2.18	1.52–3.14	< 0.001	1.79	1.17–2.73	0.007
CEA ≥ 5.0 ng/mL	2.25	1.56–3.24	< 0.001	2.00	1.31–3.02	0.001
CA 19 – 9 ≥ 37.0 ng/mL	2.08	1.42–3.03	< 0.001	1.10	0.71–1.67	0.666
Treatment						
Biliary drainage	0.70	0.49–1.00	0.053			
Combination therapy	0.70	0.48–1.01	0.058	1.08	0.69–1.73	0.716
Second-line chemotherapy	0.61	0.43–0.88	0.007			

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NLR, neutropenia leukopenia ratio; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA 19 – 9, carbohydrate antigen 19 – 9

Table 3 Grade 3 or worse adverse events

	Combination therapy (*N* = 100)		**Monotherapy (*N* = 57)**		***p*-value[‡]**
	n	**(%)**	***n***	**(%)**	
Total	79	(79)	30	(53)	0.001
Hematological adverse event	70	(70)	25	(44)	0.002
Neutropenia	77	(77)	17	(30)	< 0.001
Thrombocytopenia	18	(18)	10	(18)	1.000
Anemia	14	(14)	5	(9)	0.287
Nonhematological adverse event	23	(23)	8	(14)	0.214
Cardiac disorders	4	(4.0)	3	(5.3)	0.354
Anorexia	2	(2.0)	3	(5.3)	0.354
Sepsis	1	(1.0)	3	(5.3)	0.136
Skin rash	5	(5.0)	0	(0)	0.160
Interstitial pneumonia	3	(3.0)	0	(0)	0.554
Renal dysfunction	1	(1.0)	0	(0)	1.000
Fatigue	1	(1.0)	0	(0)	1.000
Peripheral sensory neuropathy	1	(1.0)	0	(0)	1.000
Oral mucositis	1	(1.0)	0	(0)	1.000
Febrile neutropenia	1	(1.0)	0	(0)	1.000
Others	3	(3.0)	0	(0)	0.554

[‡]Fisher's exact test

Regarding efficacy, a trend towards prolonged PFS and OS was observed in the combination therapy group compared with that in the monotherapy group. However, combination therapy was not identified as an independent prognostic factor in the multivariate analysis. Notably, combination therapy was associated with a higher incidence of grade ≥ 3 adverse events; however, treatment discontinuation due to adverse events did not significantly differ between the groups, and no treatment-related deaths occurred. Therefore, combination therapy is considered tolerable even in older patients.

The benefit of combination therapy for older patients with BTC has been indicated in a few retrospective studies because its efficacy and safety in older patients were similar to those in younger patients [13, 14, 18]. However, the participants in previous studies were younger than

those in the present study. In some studies, individuals aged > 65 years were defined as older adults, with the proportion of patients aged ≥ 75 years being < 20% [12, 19, 20]. In contrast, in the present study, we included patients with a median age of 78 years, and the oldest patient was 90 years. Furthermore, we included patients with various conditions, such as low PS or accompanying comorbidities, who were excluded from previous clinical trials.

In the present study, multivariable analysis revealed gallbladder cancer, CEA, neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP) levels as prognostic factors associated with OS. Conversely, age and treatment regimens were not associated with OS. These results suggest that combination therapy, which is the current standard treatment, is not necessarily recommended for all patients aged ≥ 75 years. Regarding safety, the rate of severe adverse events did not significantly differ between older and younger patients in a previous study [21]. However, combination therapy tends to be associated with a higher incidence of adverse events, and severe adverse events can shorten the prognosis of older patients [22]. Therefore, selecting patients who can tolerate the adverse events of combination therapy is essential.

In the present study, subgroup analysis revealed that combination therapy was beneficial for patients aged < 80 years, those with a BMI ≥ 22 kg/m^2, and those with an ECOG PS of 0. The potential for false positives due to multiple comparisons and limitations in sample size may impact these results; however, these results suggest that combination therapy is beneficial for older patients with certain characteristics. Treating older patients with cancer is complex owing to physiological limitations and individual differences [23–25], and treatment decisions based on physicians' subjective judgments regarding PS and age may lead to either overtreatment or undertreatment [26]. Therefore, using geriatric assessments, as recommended by the American Society of Clinical Oncology and the International Society of Geriatric Oncology [27, 28], to propose an appropriate regimen for each patient and making treatment decisions based on the patient's preferences is necessary.

Immune checkpoint inhibitors (ICIs) have changed cancer treatment, offering new hope to patients with various types of cancer, and have recently become available for the treatment of biliary tract cancer [29–31]. Some studies indicate that ICIs can improve overall survival (OS) in both younger and older patients, while others suggest that there is no significant survival advantage in this very elderly subgroup [32, 33]. Given these varied outcomes, the safety and effectiveness of combining ICIs with GC for older patients remain unclear. Since older patients have diverse health conditions, further research on GC plus ICI in this population is needed to better define which patients might truly benefit from this combination therapy.

This study has some limitations. First, because this was a retrospective single-center study, unintentional selection bias could not be fully excluded. Second, dosage adjustments, including initial dose reductions and interruptions, were determined at the discretion of each physician. Third, the incidence of adverse events, particularly non-hematological events, may have been underestimated. Finally, ICIs were not administered to all patients in the present study. Whether the results of the present study can be extrapolated to real-world practice in the ICI era remains uncertain [34–36]. However, ICIs are administered in addition to combination therapy; therefore, identifying patients who will benefit from combination therapy is valuable information.

Conclusions

In real-world clinical practice involving older patients with BTC who have various health conditions, there was no difference in efficacy between combination therapy and monotherapy; however, the incidence of grade ≥ 3 adverse events were higher in the combination therapy group than in the monotherapy group. These results suggest that the standard combination therapy is not necessarily recommended for all older patients with BTC. Selecting an appropriate chemotherapy regimen based on each patient's condition is essential.

Abbreviations

BTC	Biliary tract cancer
GEM	Gemcitabine
BMI	Body mass index
BSA	Body surface area
ECOG PS	Eastern Cooperative Oncology Group performance status
OS	Overall survival
PFS	Progression-free survival
DI	Dose intensity
PD	Progressive disease
ICIs	Immune checkpoint inhibitors

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14014-1.

Supplementary Material 1

Supplementary Material 2

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Author contributions

R.O., M.U. and S.K. wrote the main manuscript text.All authors were involved in reviewing the manuscript and in making the decision to submit for publication. The authors read and approved the final manuscript.

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None to declare.

Data availability
The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of the research participants; however, they are available from the corresponding author (S. Kobayashi) upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the institutional review board of the Kanagawa Cancer Center (ID: 2021-41) and was conducted according to the Declaration of Helsinki. The participants were given the opportunity to opt out of having their information published.

Consent for publication
Not applicable.

Competing interests
・ S. Kobayashi received honoraria for speakers' bureaus from AstraZeneca plc, MSD K.K., and Taiho Pharmaceutical Co., Ltd.・ M. Ueno received grants from Taiho Pharmaceutical Co., Ltd., AstraZeneca K.K., MSD K.K., Nihon Servier Co., Ltd., Ono Pharmaceutical Co., Ltd., Incyte Biosciences Japan GK, Chugai Pharmaceutical Co., Ltd., Boehringer Ingelheim GmbH, Eisai Co., Ltd., Novartis Pharma K.K., Astellas Pharma Inc., J-pharma Co., Ltd., DFP (Delta-Fly Pharma), Inc., Novocure GmbH, and Chiome Bioscience Inc., and honoraria for speakers' bureaus from Taiho Pharmaceutical Co., Ltd., AstraZeneca K.K., Yakult Honsha Co., Ltd., MSD K.K., Nihon Servier Co., Ltd., Ono Pharmaceutical Co., Ltd., Incyte Biosciences Japan GK, Chugai Pharmaceutical Co., Ltd., Boehringer Ingelheim GmbH, J-pharma Co., Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Novartis Pharma K.K.・ The other authors declare no conflicts of interest.

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