World Journal of Surgical Oncology

RESEARCH

Open Access

Efficacy and conversion outcome of chemotherapy combined with PD-1 inhibitor for patients with unresectable or recurrent gallbladder carcinoma: a real-world exploratory study

Qin-qin Liu[1,2†], Jian Yan[3†], Yan-fang Ye[4†], Cai-ni Yang[1], Zhi-jun Chen[1], Hao-ming Lin[1*], Zi-tong Zhang[5*] and Rui Zhang[1*]

Abstract

Background Gallbladder carcinoma (GBC) is an extremely aggressive tumor of the biliary tract with a bleak prognosis, and the evidence supporting the benefit of available systemic therapy for advanced GBC is scarce. Herein, this study intended to investigate the real-world outcome of chemotherapy combined with programmed death-1 (PD-1) inhibitor for the management of unresectable or recurrent GBC.

Methods From January 2018 to December 2023, consecutive patients who were treated with systematic treatment, including chemotherapy or the combination of chemotherapy plus PD-1 inhibitor, for unresectable or recurrent GBC were retrospectively identified. Clinical data regarding baseline characteristics, therapeutic response, adverse events (AEs), and oncological outcomes were collected.

Results The eligible patients were allocated to combination therapy arm ($n=46$) and mono-chemotherapy arm ($n=19$). After propensity score matching (PSM), 16 patients were allocated in each arm. The overall survival (OS) and progression-free survival (PFS) of combination therapy were marginally superior to mono-chemotherapy both before and after PSM. The combination therapy exhibited advantage over mono-chemotherapy in regards to partial response (PR) (before PSM: $P=0.009$; after PSM: $P=0.037$) and objective response rate (ORR) (before PSM: $P=0.006$;

†Qin-qin Liu, Jian Yan and Yan-fang Ye contributed equally to this work and share first authorship.

*Correspondence:
Hao-ming Lin
surgeon0001@163.com
Zi-tong Zhang
zt83583990@163.com
Rui Zhang
zhangr95@mail.sysu.edu.cn

Full list of author information is available at the end of the article

after PSM: $P=0.015$). In combined therapy cohort, 1 patient achieve a complete response, and 13 patients were assessed as appropriate for surgical excision, among which 1 patient refused further surgical intervention.

Conclusions In patients with unresectable or recurrent GBC, the combination of chemotherapy and PD-1 inhibitor as first-line therapy exhibited prolonged OS and PFS, and increased PR and ORR over those receiving chemotherapy alone, with an acceptable toxicity profile. The combination therapy may be a potential conversion therapy in unresectable GBC patients.

Keywords PD-1 inhibitor, Chemotherapy, Gallbladder carcinoma, Real-world study

Introduction

Biliary tract cancers (BTCs) represent a highly lethal malignant tumor of the liver with a reported 5-year overall survival rate of less than 20% [1]. Surgical resection remains the standard clinical care for BTC to prolong patient survival; however, the majority of the patients are not amenable to the curative option due to the highly aggressive and infiltrative nature of BTC [2, 3]. Despite radical resection of the primary tumor, approximately 60–70% of patients experienced tumor recurrence [3]. Systemic chemotherapy is regarded as a cornerstone of palliative care for unresected or metastatic disease management [4].

Based on the results derived from ABC-02 study and BT-22 study [5, 6], gemcitabine-cisplatin(GC) regime is recommended as first-line chemotherapy for the treatment of advanced BTC [7]. In ABC-02 Phase III trial, the GC group was associated with prolonged median overall survival compared with the gemcitabine group (11.7 months vs. 8.1 months, $P<0.001$) [4]. Several clinical studies were further conducted to investigate other first-line regimens for advanced BTC. The FUGA-BT (JCOG1113) randomized phase II trial using nab-paclitaxel and gemcitabine in 74 patients with advanced or metastatic cholangiocarcinoma reported a median overall survival (OS) and progression-free survival (PFS) of 12.4 and 7.7 months [8]. A phase III clinical trial demonstrated that gemcitabine plus S-1 produced non-inferior outcomes to the GC regime, with a median OS and PFS of 15.1 and 6.8 months, respectively [9]. In addition, another phase III randomized controlled trial failed to show the survival superiority of modified gemcitabine and oxaliplatin over GC in gallbladder carcinoma (GBC) patients [10]. Considering the limited efficacy of available treatment modalities, there remains a desperate need for alternative strategies for patients with advanced BTC.

Immunotherapy has attracted tremendous attention and promoted the investigation of tumor immune microenvironment in recent years, resulting in the launch of numerous clinical trials for solid tumor [11]. Disappointingly, previous studies have demonstrated the limited tumor therapeutic effects of immunotherapy as monotherapy in patients with cholangiocarcinoma [12]. The combination of immunotherapy with local-regional interventions, targeted agents, or other anti-angiogenic therapies has been proposed and has proven to provide synergistic efficacy, resulting in an increased antitumor response [13, 14]. Camrelizumab combined with gemcitabine and oxaliplatin as a first-line regimen was administrated to 37 patients with BTC in a phase II study [15]. The efficacy-evaluable patients had median PFS and OS of 6.1 and 11.8 months with a confirmed objective response (ORR) of 54%. Nevertheless, the evidence supporting chemotherapy plus immunotherapy in BTCs is sparse. Furthermore, BTCs consist of heterogeneous subpopulations with different origins, suggesting the discrepancies in tumor response to the combined therapy.

To investigate these issues, we sought to elucidate the efficacy and safety of chemotherapy alone versus chemotherapy plus programmed death-1 (PD-1) inhibitor in unresectable or recurrent GBC patients in a real-world setting.

Methods

Study design

This retrospective cohort study collected patients with unresectable or recurrent GBC who received chemotherapy alone or chemotherapy plus PD-1 inhibitor between January 2018 and June 2022 at the Sun Yat-sen Memorial Hospital. The eligibility criteria for enrollment were the following: (1) age older than 18 years; (2) histologically confirmed unresectable or recurrent GBC; (3) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1;(4) existence of measurable lesion(s) on radiological images; (5) a life expectancy longer than 12 weeks; (6) adequate organ function; (7) received systemic regimens (including chemotherapy alone or combined with PD-1 inhibitor). Patients with a previous history of other malignancies or autoimmune diseases were excluded from enrollment.

Study treatment

Relying on the medication administration records, patients were allocated to either monotherapy cohort or combination therapy cohort. Patients were prescribed one of the following chemotherapy regimens every three weeks: gemcitabine plus cisplatin, gemcitabine plus oxaliplatin, gemcitabine plus albumin-bound paclitaxel,

gemcitabine plus S-1, albumin-bound paclitaxel plus cisplatin, gemcitabine, capecitabine, or S-1. Concomitant immunotherapy consisting of sintilimab, camrelizumab, pembrolizumab, tislelizumab, toripalimab, penpulimab, or durvalumab was administered intravenously in each treatment cycle. The detailed treatment regimens were listed below (Table 1). Further treatment was discontinued on the occurrence of radiographic progression, treatment intolerance, individual refusal, or death.

Oncological outcome assessment

The available clinical information regarding patient characteristics, therapeutic response, PSF, OS, and adverse events (AEs) were archived and detected. Radiological images were reviewed and tumor responses were sorted according to the modified Response Evaluation Criteria in Solid Tumors, version 1.1 (mRECIST 1.1). The treatment-related AEs were assessed based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.02.

Table 1 Treatment regimens

Treatment regimens	Monotherapy cohort	Combined therapy cohort
gemcitabine plus cisplatin	8(42.1%)	-
gemcitabine plus oxaliplatin	6(31.6%)	-
gemcitabine plus albumin-bound paclitaxel	2(10.5%)	-
gemcitabine plus S-1	1(5.3%)	-
gemcitabine	1(5.3%)	-
capecitabine	1(5.3%)	-
sintilimab + gemcitabine plus cisplatin	-	1(2.2%)
sintilimab + gemcitabine plus oxaliplatin	-	4(6.2%)
sintilimab + gemcitabine plus S-1	-	1(2.2%)
sintilimab + gemcitabine plus albumin-bound paclitaxel	-	2(4.3%)
sintilimab + capecitabine	-	1(2.2%)
camrelizumab + gemcitabine plus cisplatin	-	2(4.3%)
camrelizumab + gemcitabine plus oxaliplatin	-	10(21.7%)
camrelizumab + gemcitabine plus albumin-bound paclitaxel	-	1(2.2%)
camrelizumab + albumin-bound paclitaxel plus cisplatin	-	1(2.2%)
camrelizumab + capecitabine	-	1(2.2%)
pembrolizumab + gemcitabine plus cisplatin	-	1(2.2%)
pembrolizumab + gemcitabine plus oxaliplatin	-	1(2.2%)
tislelizumab + S-1	-	1(2.2%)
tislelizumab + gemcitabine plus cisplatin	-	1(2.2%)
tislelizumab + gemcitabine plus oxaliplatin	-	8(17.4%)
tislelizumab + gemcitabine plus S-1	-	2(4.3%)
tislelizumab + gemcitabine plus albumin-bound paclitaxel	-	1(2.2%)
toripalimab + gemcitabine plus cisplatin	-	1(2.2%)
toripalimab + gemcitabine plus oxaliplatin	-	4(6.2%)
penpulimab + gemcitabine plus oxaliplatin	-	1(2.2%)
durvalumab + gemcitabine plus oxaliplatin	-	1(2.2%)

Statistical analysis

PSM was carried out using the following variables: gender, ECOG PS score, CA19-9, CEA, disease status, tumor number, site of metastases, and previous therapy. Body mass index (BMI) and largest tumor size were expressed as median with interquartile range. Age was as presented as mean ± standard deviation. Gender, ECOG PS score, serum carbohydrate antigen 19 – 9 (CA19-9), serum carcinoembryonic antigen (CEA), disease status, number of metastatic sites, site of metastases, and previous therapy were noted as the frequency with percentage. The age was compared with Mann-Whitney U test. Gender, ECOG PS score, CA19-9, CEA, disease status, tumor number, site of metastases, previous therapy, treatment response, adverse events were compared with Chi-square test or Fisher's Exact test. The survival analysis was carried out using the Kaplan-Meier method and the log-rank test. Results with a nominal Pvalue < 0.05 was regarded significant. Statistical Package for the Social Sciences (SPSS) 25.0 software was employed for data analysis.

Results

Patients' baseline characteristics

From January 2018 to December 2023, 65 patients with unresectable or recurrent GBC at Sun Yat-sen Memorial Hospital were available for analysis. Among them, 19 patients were treated with chemotherapy, and another 46 patients were administered chemotherapy plus immunotherapy. And there were 16 patients in each cohort after propensity score matching (PSM). Comparable baseline characteristics were observed between the two cohorts both before and after PSM (Table 2). The median age of the entire cohort was 63.0 (54.5–67.0) years, with men accounting for 58.5%. The percentage of previous abdominal surgery did not differ between the two treatment arms (52.6% vs. 28.3%, $P = 0.062$). Twenty-three patients received previous surgery for GBC. Four patients received cholecystectomy; six patients received cholecystectomy and liver segments S4b and S5 resection; two patients received cholecystectomy, liver segments S4b and S5 resection, and omental mass excision; one patient received cholecystectomy and liver segments S4, S5, S6, and S7 resection; one patient received cholecystectomy and liver segment S5 resection; one patient received cholecystectomy and liver segments S4, S5, S6, and S8 resection; one patient received cholecystectomy, liver segments S4b and S5 resection, and subtotal gastrectomy; one patient received cholecystectomy, liver segments S4b, S5, S6, S7, and S8 resection, and omental mass excision; one patient received cholecystectomy, liver segments S2 and S3 resection, and pancreaticoduodenectomy; one

Table 2 Patient characteristics by treatment cohort

Variables	before PSM			after PSM		
	Monotherapy cohort	Combined therapy cohort	*P* value	Monotherapy cohort	Combined therapy cohort	*P* value
	n = 19	*n* = 46		*n* = 16	*n* = 16	
Age, years	63.0(52.0–68.0)	62.5(55.0–67.0)	0.965	63.0(50.5–67.5)	60.5(53.0-64.8)	0.539
Gender			0.085			0.723
Female	11(57.9%)	16(34.8%)		9(56.3%)	8(50.0%)	
Male	8(42.1%)	30(65.2%)		7(43.8%)	8(50.0%)	
ECOG PS score			0.562			1.000
0	11(57.9%)	23(50.0%)		9(56.3%)	9(56.3%)	
1	8(42.1%)	23(50.0%)		7(43.8%)	7(43.8%)	
CA19-9			0.166			1.000
Normal (≤ 37 U/ml)	11(57.9%)	18(39.1%)		9(56.3%)	9(56.3%)	
Abnormal (> 37 U/ml)	8(42.1%)	28(60.9%)		7(43.8%)	7(43.8%)	
CEA			0.260			1.000
Normal (≤ 5 ng/mL)	12(63.2%)	22(47.8%)		11(68.8%)	11(68.8%)	
Abnormal (> 5 ng/mL)	7(36.8%)	24(52.2%)		5(31.3%)	5(31.3%)	
Disease status			0.083			1.000
Locally advanced[16]	0(0.0%)	6(13.0%)		0(0.0%)	0(0.0%)	
Metastatic	9(47.4%)	27(58.7%)		8(50.0%)	8(50.0%)	
Recurrent	10(52.6%)	13(28.3%)		8(50.0%)	8(50.0%)	
Tumor number			0.789			1.000
1	6(31.6%)	13(28.3%)		6(37.5%)	6(37.5%)	
≥ 2	13(68.4%)	33(71.7%)		10(62.5%)	10(62.5%)	
Site of metastases						
Liver	14(73.7%)	30(65.2%)	0.507	12(75.0%)	12(75.0%)	1.000
Lymph node	5(26.3%)	23(50.0%)	0.079	5(31.3%)	7(43.8%)	0.465
Peritoneum	4(21.1%)	6(13.0%)	0.663	3(18.8%)	1(6.3%)	0.600
Lung	3(15.8%)	4(8.7%)	0.408	1(6.3%)	3(18.8%)	0.600
Bone	0(0.0%)	2(4.3%)	1.000	0(0.0%)	0(0.0%)	1.000
Previous therapy						
Surgery	10(52.6%)	13(28.3%)	0.062	8(50.0%)	8(50.0%)	1.000
ablation	1(5.3%)	0(0.0%)	0.292	0(0.0%)	0(0.0%)	1.000
TACE	0(0.0%)	1(2.2%)	1.000	0(0.0%)	0(0.0%)	1.000

ECOG PS, Eastern Cooperative Oncology Group performance status; CA199, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; TACE, Transcatheter arterial chemoembolization

patient received cholecystectomy, liver segments S4b, S5, and S7 resection, and omental mass excision; one patient received liver segments S5 and S8 resection, colonic mass resection, and right adrenal mass excision; one patient received liver segments S5, S6, and S8 resection and omental mass excision; one patient received cholecystectomy and left hemihepatectomy; and one patient received cholecystectomy and pancreaticoduodenectomy. One patient received previous ablation in the monotherapy cohort, and one patient received previous TACE in the combined therapy cohort.

Treatment response

The treatment response according to mRESIST criteria was evaluated and summarized in Table 3. Patients assigned to the monotherapy cohort received a confirmed median of 2 (2–4) treatment cycles compared with 3.5 (2–5) cycles in the combined therapy cohort ($P = 0.073$). Before PSM, no patients achieved CR (complete response), 1 (5.3%) patients achieved PR (partial response), 10 (52.6%) patients achieved SD (stable disease), and 8 (42.1%) patients achieved PD in the monotherapy cohort. 1 (2.2%) patient achieved CR, 17 (37.0%) patients achieved PR, 19 (41.3%) patients achieved SD, and 9 (19.6%) patients achieved PD in the combined therapy cohort. The monotherapy cohort had an ORR of 5.3%, which was significantly lower than to that of the combined therapy cohort (39.1%, $P = 0.006$). In addition, no significant difference was noted in terms of DCR (disease control rate), with 57.9% in the monotherapy cohort and 80.4% in the combined therapy cohort ($P = 0.116$). After PSM, no patients achieved CR, 1 (6.3%) patients achieved PR, 7 (43.8%) patients achieved SD, and 8 (50.0%) patients achieved PD in the monotherapy

Table 3 Treatment response evaluation

Response	before PSM			after PSM		
	Monotherapy cohort	Combined therapy cohort	*P* value	Monotherapy cohort	Combined therapy cohort	*P* value
Complete response	0(0.0%)	1(2.2%)	1.000	0(0.0%)	1(6.3%)	1.000
Partial response	1(5.3%)	17(37.0%)	0.009	1(6.3%)	7(43.8%)	0.037
Stable disease	10(52.6%)	19(41.3%)	0.403	7(43.8%)	5(31.3%)	0.465
Progressive disease	8(42.1%)	9(19.6%)	0.116	8(50.0%)	3(18.8%)	0.063
Objective response rate	1(5.3%)	18(39.1%)	0.006	1(6.3%)	8(50.0%)	0.015
Disease control rate	11(57.9%)	37(80.4%)	0.116	8(50.0%)	13(81.3%)	0.135

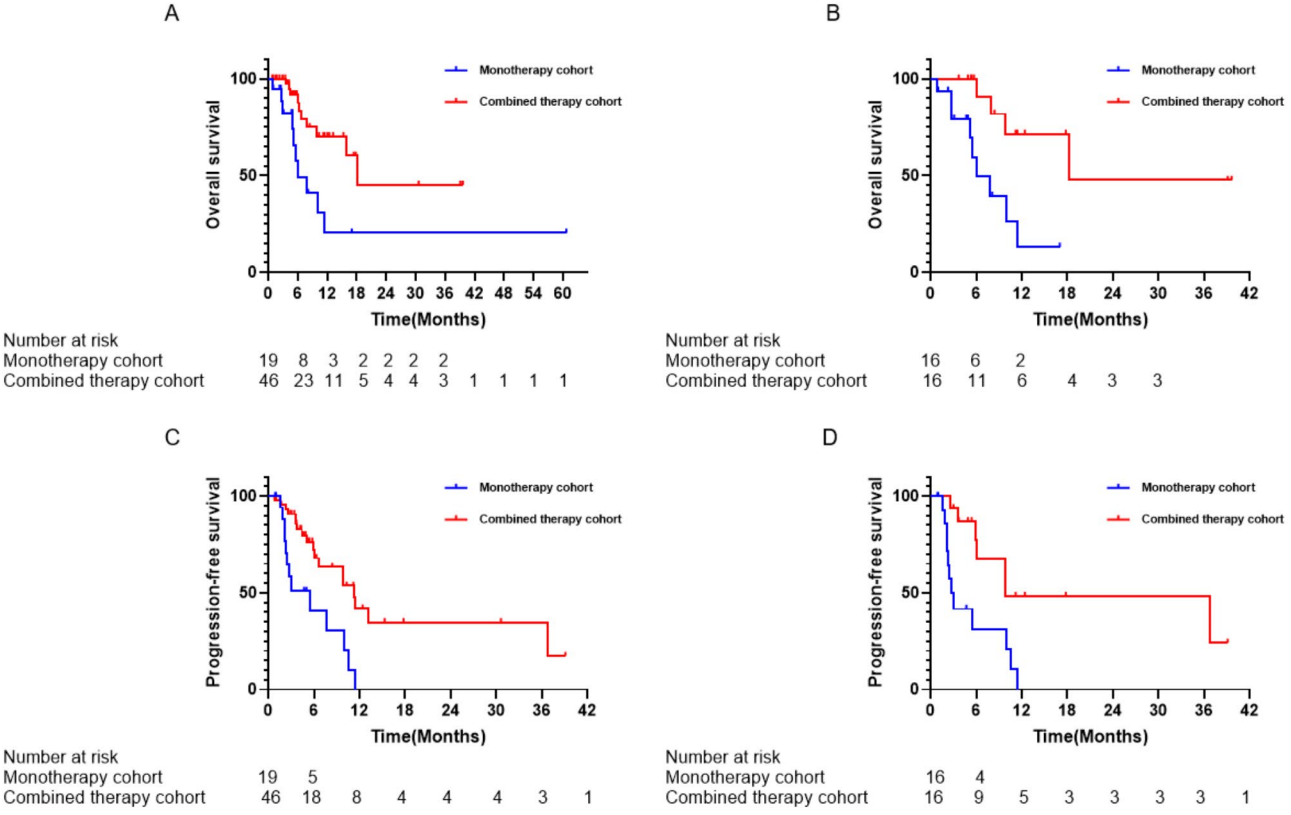

Fig. 1 Survival curves for OS (**A**) and PFS (**B**) before PSM, and survival curves for OS (**C**) and PFS (**D**) after PSM. OS, overall survival; PFS, progression-free survival

cohort. 1 (6.3%) patient achieved CR, 7 (43.8%) patients achieved PR, 5 (31.3%) patients achieved SD, and 3 (18.8%) patients achieved PD in the combined therapy cohort. The monotherapy cohort had a lower ORR than the combined therapy cohort (6.3% vs. 50.0%, $P=0.015$). DCR was comparable between the two cohorts (50.0% vs. 81.3%, $P=0.135$).

Survival outcomes

The median follow-up for the entire cohort was 5.5(3.7–10.8) months. Compared with the monotherapy cohort, the combined therapy cohort had significantly prolonged OS both before and after PSM (Figs. 1A and 18.2 months vs. 6.1 months, $P=0.006$; Fig. 1B, **18**.2 months vs. 6.1 months, $P=0.004$, respectively). Before PSM, 13 patients in the monotherapy cohort and 18 patients in the combined therapy cohort experienced PFS events, and 12 patients in the monotherapy cohort and 7 patients in the combined therapy cohort experienced PFS events after PSM. The combined therapy significantly improved the median PFS versus the monotherapy both before and after PSM (Figs. 1C and 11.3 vs. 5.5 months, $P=0.001$; Fig. 1D, **9**.8 vs. 2.7 months, $P=0.002$, respectively).

Toxicity

AEs of the two groups were recorded and displayed in Table 4. Before PSM, 15(78.9%) patients receiving chemotherapy experienced all-grade toxicities versus 35(76.1%) patients receiving chemotherapy plus immunotherapy ($P=1.000$). Anemia (68.4%) was the most

Table 4 Adverse events in the two cohorts

	before PSM						after PSM					
	Any grade		*P*	Grade 3–4		*P*	Any grade		*P*	Grade 3–4		*P*
	Monotherapy cohort	Combined therapy cohort		Monotherapy cohort	Combined therapy cohort		Monotherapy cohort	Combined therapy cohort		Monotherapy cohort	Combined therapy cohort	
Decreased appetite	6(31.6%)	8(17.4%)	0.350	0(0.0%)	0(0.0%)	-	6(37.5%)	3(18.8%)	0.433	0(0.0%)	0(0.0%)	-
Pruritus	2(10.5%)	0(0.0%)	0.082	0(0.0%)	0(0.0%)	-	2(12.5%)	0(0.0%)	0.484	0(0.0%)	0(0.0%)	-
Rash	1(5.3%)	0(0.0%)	0.292	0(0.0%)	0(0.0%)	-	1(6.3%)	0(0.0%)	1.000	0(0.0%)	0(0.0%)	-
Fatigue	1(5.3%)	1(2.2%)	0.502	0(0.0%)	0(0.0%)	-	1(6.3%)	0(0.0%)	1.000	0(0.0%)	0(0.0%)	-
Nausea/Vomiting	5(26.3%)	14(30.4%)	0.740	0(0.0%)	0(0.0%)	-	5(31.3%)	2(12.5%)	0.394	0(0.0%)	0(0.0%)	-
Abdominal distention	1(5.3%)	4(8.7%)	1.000	0(0.0%)	0(0.0%)	-	1(6.3%)	0(0.0%)	1.000	0(0.0%)	0(0.0%)	-
Alopecia	1(5.3%)	0(0.0%)	0.292	0(0.0%)	0(0.0%)	-	1(6.3%)	0(0.0%)	1.000	0(0.0%)	0(0.0%)	-
Fever	2(10.5%)	3(6.5%)	0.625	0(0.0%)	0(0.0%)	-	2(12.5%)	2(12.5%)	1.000	0(0.0%)	0(0.0%)	-
Pneumonia	1(5.3%)	1(2.2%)	0.502	1(5.3%)	1(2.2%)	0.502	1(6.3%)	1(6.3%)	1.000	1(6.3%)	1(6.3%)	1.000
Gastrointestinal hemorrhage	2(10.5%)	3(6.5%)	0.625	1(5.3%)	0(0.0%)	0.292	2(12.5%)	1(6.3%)	1.000	1(6.3%)	0(0.0%)	1.000
Proteinuria	1(5.3%)	1(2.2%)	0.502	0(0.0%)	0(0.0%)	-	1(6.3%)	0(0.0%)	1.000	0(0.0%)	0(0.0%)	-
Hypothyroidism	1(5.3%)	3(6.5%)	1.000	0(0.0%)	0(0.0%)	-	1(6.3%)	2(12.5%)	1.000	0(0.0%)	0(0.0%)	-
Leukopenia	3(15.8%)	9(19.6%)	0.996	0(0.0%)	1(2.2%)	1.000	3(18.8%)	4(25.0%)	1.000	0(0.0%)	1(6.3%)	1.000
Neutropenia	3(15.8%)	8(17.4%)	1.000	1(5.3%)	1(2.2%)	0.502	3(18.8%)	3(18.8%)	1.000	1(6.3%)	0(0.0%)	1.000
Anemia	13(68.4%)	20(43.5%)	0.067	5(26.3%)	8(17.4%)	0.633	11(68.8%)	8(50.0%)	0.473	5(31.3%)	1(6.3%)	0.172
Thrombocytopenia	1(5.3%)	6(13.0%)	0.663	0(0.0%)	2(4.3%)	1.000	1(6.3%)	3(18.8%)	0.600	0(0.0%)	2(12.5%)	0.484
AST elevation	1(5.3%)	8(17.4%)	0.372	0(0.0%)	3(6.5%)	0.550	1(6.3%)	3(18.8%)	0.600	0(0.0%)	2(12.5%)	0.484
ALT elevation	1(5.3%)	8(17.4%)	0.372	1(5.3%)	5(10.9%)	0.662	1(6.3%)	4(25.0%)	0.333	1(6.3%)	4(25.0%)	0.333

AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 5 Characteristics of converted patients

Variables	patients(*n*%)
Baseline characteristics	
Age, years	61.7 ± 8.9
Gender	
Female	8(66.7%)
Male	4(33.3%)
ECOG PS score	
0	7(58.3%)
1	5(41.7%)
CA19-9	
Normal (≤ 37 U/ml)	5(41.7%)
Abnormal (> 37 U/ml)	7(58.3%)
CEA	
Normal (≤ 5 ng/mL)	6(50.0%)
Abnormal (> 5 ng/mL)	6(50.0%)
Disease status	
Locally advanced	2(16.7%)
Metastatic	7(58.3%)
Recurrent	3(25.0%)
Tumor number	
1	3(25.0%)
≥ 2	9(75.0%)
Site of metastases	
Liver	8(66.7%)
Lymph node	6(50.0%)
Peritoneum	1(8.3%)
Previous surgery	3(25.0%)
Perioperative outcomes	
Operative time, min	425.3 ± 136.4
Blood loss, mL	147.0 ± 98.2
R0 resection	10(83.3%)
ASA grade	
II	7(58.3%)
III	5(41.7%)
Intraoperative transfusion	2(16.7%)
Recurrence	3(25.0%)
Perioperative mortality	1(8.3%)

common AEs of any grade in the monotherapy cohort, followed by decreased appetite (31.6%), and nausea/vomiting (26.3%). The most frequent toxicities experienced with the chemotherapy plus immunotherapy included anemia (43.5%), nausea/vomiting (30.4%), and leukopenia (19.6%). Grade 3/4 AEs were noted in 6 (31.6%) and 16 (34.8%) patients in the monotherapy cohort and combined therapy cohort, with anemia being the most commonly reported AEs in both groups. There was no apparent difference with regard to medication discontinuation due to serious AEs, with 6 (31.6%) patients in the monotherapy cohort and 16 (34.8%) patients in the combined therapy cohort ($P = 0.804$). No AE-induced death was observed in the study. After PSM, all-grade toxicities were comparable between the two group, with 15(81.3%) in the monotherapy cohort and 11(68.8%) in the combined therapy cohort ($P = 0.685$). Anemia (68.8%) was the most common AEs of any grade in the monotherapy cohort, followed by decreased appetite (37.5%), and nausea/vomiting (31.3%). The most frequent toxicities experienced with the chemotherapy plus immunotherapy included anemia (50.0%), ALT elevation (25.0%), and leukopenia (25.0%). 6 (37.5%) participants in the monotherapy cohort and 7 (43.8%) participants in the combination therapy cohort experienced Grade 3 or 4 adverse events. No significant difference was observed in the medication discontinuation between the two cohort, with 6 (37.5%) patients in the monotherapy cohort and 7 (43.8%) patients in the combined therapy cohort ($P = 1.000$).

Conversion outcome

In the combined therapy group, 1 patient was assessed to have achieved CR, and 13 patients were evaluated as suitable candidates for curative surgery. Among the 13 patients, 12 converted patients received surgical resection and 1 patient refused further surgical intervention. Five patients received cholecystectomy and liver segments S4b and S5 resection; one patient received cholecystectomy, liver segments S4b and S5 resection, and distal gastrectomy; one patient received cholecystectomy, liver segments S4b and S5 resection, partial resection of the transverse colon, and omental mass excision; one patient received cholecystectomy, liver segments S4b and S5 resection, and pancreaticoduodenectomy; one patient received cholecystectomy and liver segment S5 resection; one patient received cholecystectomy and right hemihepatectomy; one patient received retroperitoneal lymph node dissection; and one patient received liver central lobectomy. Table 5 displayed the characteristics of the 12 patients. After a median of 3.8 ± 1.1 treatment cycles, 11 patients achieved PR, and 1 patient achieved SD. Among them, 10 patients underwent R0 resection and 2 patients underwent R1 resection. And 2 patients demonstrated a pathological complete response (PCR). Following a median follow-up of 5.6(1.1–12.9) months, 9 patients survived without any signs of tumor recurrence, 1 patient died during perioperative period, and 2 patients had tumor relapse. The patient who achieved CR experienced tumor recurrence at 30.1 months follow-up from diagnosis of CR to recurrence.

ECOG PS, Eastern Cooperative Oncology Group performance status; CA199, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; ASA, American Society of Anesthesiologists.

Discussion

The employment of immunotherapy has been proven instrumental in improving the efficiency of advanced malignant neoplasms treatment, promoting its expanded indications and adoption in numerous clinical guidelines.

Our present study assessed the antitumor efficiency of chemotherapy plus PD-1 inhibitor compared with chemotherapy in first-line setting for patients with unresectable or recurrent GBC, and significantly prolonged PFS and OS, as well as increased PR and ORR were noted in the combined therapy cohort. In addition, 1 patient achieved CR, and 12 converted patients received further surgical resection in the combined therapy group. Our study primarily focused on the therapeutic efficacy and conversion outcomes of the combination of chemotherapy and PD-1 inhibitor specifically within the advanced GBC population, providing a unique perspective.

With the occult nature of GBC, most GBC are frequently developed as late-stage neoplastic lesions at detection, and great tumor burden and disseminated disease hinder the resectability rates. Patients suffering from GBC are often enrolled in palliative therapeutic plans due to inevitable rapid recurrence following complete resection and unexpected metastatic status. Although gemcitabine-based chemotherapy remains the first-line regime for advanced BTC, the survival benefits are moderate with relatively low tumor response [5, 16]. The newly established guidelines incorporated durvalumab plus gemcitabine and cisplatin into first-line regime for BTC and implied the synergistic effects of immunotherapy and chemotherapy in the treatment of BTC [17]. In despite of gratifying results of immunotherapy in BTC, the majority of clinical trials involved different cholangiocarcinoma subtypes, ignoring the potential heterogeneity of different tumor types [18, 19]. The previous experience demonstrated that GBC was an extremely aggressive subtype of BTC. Notably, few studies have carried out separate analysis on the efficacy of chemotherapy plus PD-1 inhibitor specifically for GBC patients, thus neglecting the heterogeneity inherent in BTC.

Despite the fact that previous investigators have highlighted the potential synergistic effects of chemotherapy plus PD-1 inhibitor for advanced BTC, the impact of tumor subtype on therapeutic benefits is obscure and GBC is rarely mentioned in most existing medical literatures [20, 21]. Thus, a focused analysis of subpopulation with GBC was conducted to ascertain the practical value, and the combination therapy was correlated with prominent survival advantages and a relatively minor increase in tumor response. According to the current results, the ORR and DCR of the combination therapy were 39.1% and 80.4%, which was similar to data from Chen et al. [18] However, the DCR of combined therapy cohort did not meet the theoretical expectation of an improved antitumor response when compared to monotherapy cohort. The probable explanation for the discrepant response might lie in the extremely small amount of GBC involved in the study. Meanwhile, the combination therapy was applied as first-line oncological treatment and 90.8% of GBC patients enrolled in our study were metastatic or recurrent. The moderate tumor response was presumably due to a trend toward higher tumor burden in the combined therapy cohort with 71.7% of patients with more than one lesion. The improved PR and ORR implied the combination therapy might convert an unresectable GBC into a resectable one. Notably, 1 patient achieved CR, and 12 patients received subsequent surgical removal in the combination therapy cohort. However, the patient who achieved CR presented tumor recurrence after 30.1 months follow-up. These data might give a hint on future clinical trial design with appropriate patient enrollment, rational therapeutic regimens and optimization of postoperative adjuvant treatment for better tumor control and increased conversion therapy rates.

BTCs are composed of distinct subtypes originating from different anatomical sites, which may be the consequence of heterogeneous tumor response to combined chemotherapy plus immunotherapy [22, 23]. The chemotherapeutic agents synergize with immunotherapy to exhibit immunostimulatory effects by promoting CD8 + T cells infiltration and activation, facilitating sustained cytotoxic damage to tumors [24–26]. Nonetheless, the detailed underlying mechanism of synergistic antitumor effects remains to be elicited [27]. The changes of PD-L1 expression following systemic treatment have proved to be a predictive biomarker of tumor response and oncological outcomes. Oh et al. demonstrated that PD-L1 expression in immune cells was more frequently up-regulated following GC plus immunotherapy than chemotherapy with GC [28]. Additional studies may further uncover the changes in tumor immune microenvironment following the combined chemotherapy and immunotherapy, and determine the robust predictive biomarker and the potential candidates for the treatment to guide therapeutic decision-making.

In close agreement with the historical literatures, the hematologic AEs were most frequently recorded in our present findings, with anemia as the prevailing symptom (68.4% in the monotherapy cohort and 43.5% in the combined therapy cohort) [20, 29]. The increase of ALT and AST elevation in patients receiving combination therapy was documented, possibly owing to the introduction of immunotherapy. Although the study was underpowered to indicate this difference, these results still suggest a crucial role for hepatic function monitoring during the immunotherapy period. The generally acceptable AEs of two treatment arms prompt future clinical investigations regarding the accessibility of immunotherapy-based systemic regimes.

Admittedly, several potential limitations related to the clinical data should be taken into consideration. Limited cases with heterogeneous therapeutic regimes were incorporated in this present study. In addition, the

retrospective analysis was subject to single institutional bias and restricted the reliability of our preliminary conclusions. Also, heterogeneous surgical procedures performed on GBC patients might introduce substantial bias. Therefore, formal clinical researches are imperative to generalize the clinical application of the combination therapy and determine feasible regimes for special subpopulations.

In conclusion, chemotherapy plus PD-1 inhibitor conferred improved antitumor effects regarding advantageous survival prognosis and favorable conversion outcome compared with single-agent chemotherapy. Additional investigation steps toward the implementation of combination therapy for advanced GBC in clinical practice are warranted to advance our research to design the optimum therapeutic regime. Exploring the value of conversion therapy is beneficial for personalized treatment plans, as combination therapies may offer patients with potentially curative surgical options.

Acknowledgements
None.

Author contributions
Qin-qin Liu: Data curation (Equal), Formal analysis (Equal), Methodology (Lead), Software (Equal), Writing– original draft (Lead), Writing– review & editing (Equal); Jian Yan: Data curation (Equal); Yan-fang Ye: Methodology (Lead); Cai-ni Yang: Data curation (Equal); Zhi-jun Chen: Data curation (Equal); Hao-ming Lin: Data curation (Equal); Zitong Zhang: Conceptualization (Equal); Rui Zhang: Conceptualization (Equal), Writing– review & editing (Equal).

Funding
This work was supported by the Special Research Foundation of the National Nature Science Foundation of China (82273476), the Guangdong Basic and Applied Basic Research Foundation (2023A1515010188); Guangzhou Science and Technology Foundation（2023A03J0701）; Fundamental Research Funds for the Central Universities, Sun Yat-sen University 24xkjc035.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Sun Yat-sen Memorial Hospital. The Ethics Committee of Sun Yat-sen Memorial Hospital waived the requirement for written informed consent for this study due to its retrospective nature.

Competing interests
The authors declare no competing interests.

Author details
[1]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Department of Biliary-Pancreatic Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510120, China
[2]Department of Hepatobiliary Surgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, Guangdong, China
[3] Department of Hepatobiliary surgery, the Third Affiliated Hospital of Southern Medical University, Guangzhou, Guangdong, China
[4]Clinical Research Design Division, Sun Yat-sen Memorial Hospital, Guangzhou, China
[5]Houjie Hospital of Dongguan, Dongguan, China

Received: 3 September 2024 / Accepted: 3 February 2025
Published online: 28 February 2025

References

1. Lamarca A, Palmer DH, Wasan HS, 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 May. 2021;22(5):690–701. https://doi.org/10.1016/s1470-2045(21)00027-9
2. Ishihara S, Horiguchi A, Miyakawa S, Endo I, Miyazaki M, Takada T. Mar. Biliary tract cancer registry in Japan from 2008 to 2013. Journal of hepato-biliary-pancreatic sciences. 2016;23(3):149– 57. https://doi.org/10.1002/jhbp.314
3. Lamarca A, Edeline J, McNamara MG, et al. Current standards and future perspectives in adjuvant treatment for biliary tract cancers. Cancer Treat Rev Mar. 2020;84:101936. https://doi.org/10.1016/j.ctrv.2019.101936
4. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New Horizons for Precision Medicine in biliary tract cancers. Cancer Discovery Sep. 2017;7(9):943–62. https://doi.org/10.1158/2159-8290.Cd-17-0245
5. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med Apr. 2010;8(14):1273–81. https://doi.org/10.1056/NEJMoa0908721
6. Okusaka T, Nakachi K, Fukutomi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J cancer Aug. 2010;10(4):469–74. https://doi.org/10.1038/sj.bjc.6605779
7. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary cancers, Version 2.2021, NCCN Clinical Practice guidelines in Oncology. J Natl Compr Cancer Network: JNCCN May. 2021;1(5):541–65. https://doi.org/10.6004/jnccn.2021.0022
8. Sahai V, Catalano PJ, Zalupski MM, et al. Nab-Paclitaxel and Gemcitabine as First-line treatment of Advanced or Metastatic Cholangiocarcinoma: a phase 2 clinical trial. JAMA Oncol Dec. 2018;1(12):1707–12. https://doi.org/10.1001/jamaoncol.2018.3277
9. Morizane C, Okusaka T, Mizusawa J, 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 Dec. 2019;1(12):1950–8. https://doi.org/10.1093/annonc/mdz402
10. Sharma A, Kalyan Mohanti B, Pal Chaudhary S, et al. Modified gemcitabine and oxaliplatin or gemcitabine + cisplatin in unresectable gallbladder cancer: results of a phase III randomised controlled trial. Eur J Cancer Dec. 2019;123:162–70. https://doi.org/10.1016/j.ejca.2019.10.004
11. Chen X, Wang D, Liu J, et al. Genomic alterations in biliary tract cancer predict prognosis and immunotherapy outcomes. J Immunotherapy cancer Nov. 2021;9(11). https://doi.org/10.1136/jitc-2021-003214
12. Rizzo A, Ricci AD, Brandi G. PD-L1, TMB, MSI, and other predictors of response to Immune checkpoint inhibitors in biliary Tract Cancer. Cancers Feb. 2021;1(3). https://doi.org/10.3390/cancers13030558
13. Hack SP, Verret W, Mulla S, et al. IMbrave 151: a randomized phase II trial of atezolizumab combined with bevacizumab and chemotherapy in patients with advanced biliary tract cancer. Therapeutic Adv Med Oncol. 2021;13:17588359211036544. https://doi.org/10.1177/17588359211036544
14. Kelley RK, Bridgewater J, Gores GJ, Zhu AX. Systemic therapies for intrahepatic cholangiocarcinoma. J Hepatol Feb. 2020;72(2):353–63. https://doi.org/10.1016/j.jhep.2019.10.009
15. Chen X, Wu X, Wu H, et al. Camrelizumab plus Gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. J Immunother Cancer Nov. 2020;8(2). https://doi.org/10.1136/jitc-2020-001240
16. Feng K, Liu Y, Zhao Y, et al. Efficacy and biomarker analysis of nivolumab plus gemcitabine and cisplatin in patients with unresectable or metastatic biliary tract cancers: results from a phase II study. J Immunother Cancer Jun. 2020;8(1). https://doi.org/10.1136/jitc-2019-000367
17. Oh D-Y, He AR, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced biliary tract Cancer. NEJM Evid. 2022;1(8):EVIDoa2200015. https://doi.org/10.1056/EVIDoa2200015
18. Chen X, Qin S, Gu S, et al. Camrelizumab plus oxaliplatin-based chemotherapy as first-line therapy for advanced biliary tract cancer: a multicenter, phase 2 trial. Int J Cancer Dec. 2021;1(11):1944–54. https://doi.org/10.1002/ijc.33751
19. Ueno M, Ikeda M, Morizane C, et al. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1

study. Lancet Gastroenterol Hepatol Aug. 2019;4(8):611–21. https://doi.org/10.1016/s2468-1253(19)30086-x
20. Gou M, Zhang Y, Liu T, et al. PD-1 inhibitors could improve the efficacy of Chemotherapy as First-Line treatment in biliary tract cancers: a propensity score matching based analysis. Front Oncol. 2021;11:648068. https://doi.org/10.3389/fonc.2021.648068
21. Zhao S, Guo XG, Zhang D, et al. First-line chemotherapy or in combination with programmed cell death protein-1 antibody in patients with metastatic or recurrent biliary tract cancer. J Gastroenterol Hepatol Dec. 2021;36(12):3541–7. https://doi.org/10.1111/jgh.15668
22. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. Nat Genet Sep. 2015;47(9):1003–10. https://doi.org/10.1038/ng.3375
23. Yoon JG, Kim MH, Jang M, et al. Molecular characterization of biliary Tract Cancer predicts chemotherapy and programmed death 1/Programmed death-ligand 1 blockade responses. Hepatol (Baltimore Md) Oct. 2021;74(4):1914–31. https://doi.org/10.1002/hep.31862
24. Principe N, Aston WJ, Hope DE, et al. Comprehensive Testing of Chemotherapy and Immune Checkpoint Blockade in Preclinical Cancer models identifies Additive combinations. Front Immunol. 2022;13:872295. https://doi.org/10.3389/fimmu.2022.872295
25. Iida Y, Harashima N, Motoshima T, Komohara Y, Eto M, Harada M. Contrasting effects of cyclophosphamide on anti-CTL-associated protein 4 blockade therapy in two mouse tumor models. Cancer Sci Oct. 2017;108(10):1974–84. https://doi.org/10.1111/cas.13337
26. Wu J, Waxman DJ. Immunogenic chemotherapy: dose and schedule dependence and combination with immunotherapy. Cancer Lett Apr. 2018;10:419:210–21. https://doi.org/10.1016/j.canlet.2018.01.050
27. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of Conventional Chemotherapy and targeted Anticancer agents. Cancer Cell Dec. 2015;14(6):690–714. https://doi.org/10.1016/j.ccell.2015.10.012
28. Oh DY, Lee KH, Lee DW, et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. Lancet Gastroenterol Hepatol Jun. 2022;7(6):522–32. https://doi.org/10.1016/s2468-1253(22)00043-7
29. Sun D, Ma J, Wang J, et al. Anti-PD-1 therapy combined with chemotherapy in patients with advanced biliary tract cancer. Cancer Immunol Immunotherapy: CII Sep. 2019;68(9):1527–35. https://doi.org/10.1007/s00262-019-02386-w

Publisher's note