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Experience With Anti-PD-1 Antibody, Camrelizumab, Monotherapy for Biliary Tract Cancer Patients and Literature Review

Tian Shen, MD[1], Shanhua Zheng, MD[1], Lei Geng, PhD[1], Zhengtao Liu, PhD[1], Jun Xu, PhD[1], Bingyi Lin, PhD[1], Junjie Qian, PhD[1], and Shusen Zheng, MD, PhD[1]

Abstract

Background: Novel immunotherapy is one of the options for advanced biliary tract cancer (BTC) patients who are traditionally intolerant to chemotherapy. However, clinical evidence for single immunotherapy with pembrolizumab or nivolumab is limited. The present study assessed the safety and efficiency of the anti-PD-1 antibody, camrelizumab, as monotherapy in patients with unresectable or recurrent BTC. **Methods:** A retrospective evaluation was conducted among 4 patients with BTC, including 2 with intrahepatic cholangiocellular carcinoma (ICC), one with extrahepatic bile duct cancer, and one with gallbladder cancer. The patients with unresectable or recurrent BTC were refractory or intolerant to gemcitabine plus cisplatin treatment regimens and received at least one intravenous dose (3 mg/kg) of camrelizumab monotherapy every 3 weeks. Gene sequencing analysis was also performed for biomarker screening. Patient reaction was evaluated according to modified response evaluation criteria in solid tumor (RECIST) version 1.1, progression-free survival (PFS), and toxicity. **Results:** In this cohort, 1 patient with recurrent ICC had a positive response to treatment, with a substantial tumor size reduction in liver and lung metastases verified using a radiological test after receiving 3 cycles of camrelizumab. The PFS was 4.9 months. The remaining 3 patients showed no response to treatment and experienced disease progression. RNA sequence analysis didn't found high expression on genes that related to PD-L1, microsatellite instability, tumor mutation burden, and DNA mismatch repair in these patients. Grade 3 treatment-related adverse event was observed in 1 patient. **Conclusions:** Anti-PD-1 antibody camrelizumab had a manageable safety profile in patients with advanced BTC. This initial assessment of camrelizumab monotherapy provides effective evidence for patients with refractory BTC in biomarker-unselected patients.

Keywords

anti-PD-1, camrelizumab, efficacy, biliary tract cancer, monotherapy

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Introduction

Biliary tract cancer (BTC) is a highly aggressive malignant tumor, which includes intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gallbladder cancer (GBC), and ampulla of Vater cancer. BTC affects about 2 out of 100,000 individuals with worldwide variation,[1] accounting for 3% of all gastric tumors.[2] BTC does not have specific clinical symptoms in early stages, and therefore, most patients are diagnosed at advanced stages of the disease.[3] Surgery is only available for patients with resectable BTC. Furthermore, recurrence also affects the efficiency of surgical treatment in these patients. Prognosis in patients with BTC is usually poor. Especially in patients with unresectable BTC, the 5-year survival rate ranges from 5% to 10%, with median survival time of about 6 months.[4-6]

Currently, many strategies have been adopted for BTC treatment.[7,8] Systemic chemotherapy with combined cisplatin and

[1] Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Corresponding Author:
Shusen Zheng, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Key Laboratory of Combined Multi-organ Transplantation, Ministry of Public Health, First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China.
Email: shusenzheng@zju.edu.cn

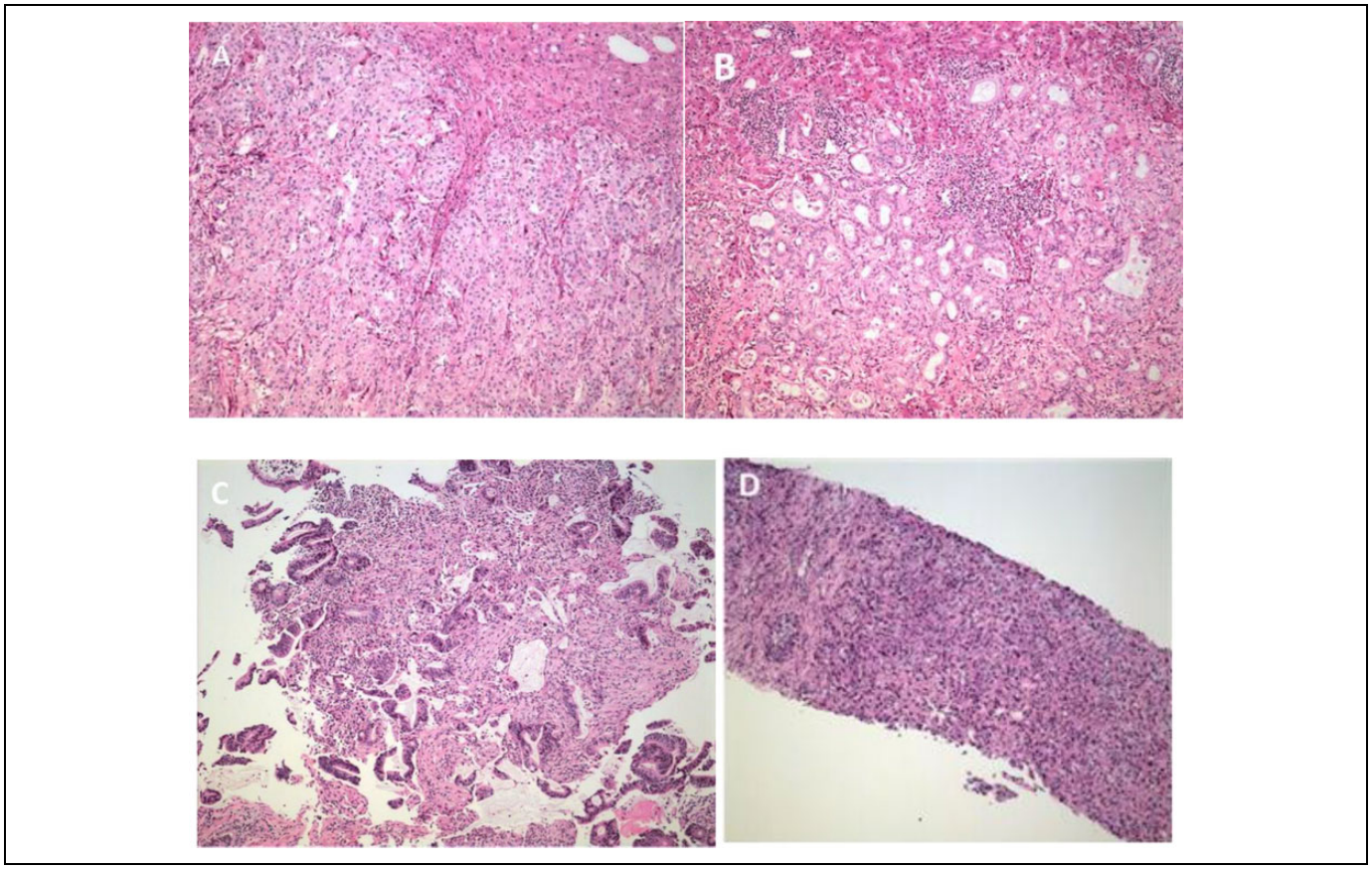

Figure 1. H&E staining of tumor tissue in formalin-fixed, paraffin-embedded sections provides orientation, Magnification ×100. A: ICC differentiated adenocarcinoma ICC, B: ICC moderately differentiated adenocarcinoma, C: common bile duct cancer moderately differentiated adenocarcinoma, D: gallbladder cancer poorly differentiated adenocarcinoma.

gemcitabine has become a standard treatment for patients with unresectable or recurrent BTC.[9] However, its efficacy is unsatisfactory and worthy of improvement. Its objective response rate (ORR) is only 20% and has a poor survival rate.[10-12] A phase II trial on second-line therapy found the ORR to be 7.7%, with mean progression-free survival (PFS) of 3.2 months and mean overall survival (OS) of 7.2 months for gemcitabine-cisplatin combined chemotherapy.[13] Thus, traditional chemotherapy seems to reach a plateau with lower ORR and poor prognosis in advanced BTC.

Recently, immune checkpoint inhibitors (ICIs) have demonstrated remarkable efficacy in many types of malignancies.[14] In general, ICIs include monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death-1 (PD1), and PD1 ligand (PD-L1). PD-1 is expressed by activated T cells and PD-L1 is expressed by tumor cells and immunocytes. Monoclonal antibody against PD-1 inhibits PD-L1 and PD-1 binding, which enhances tumor immune response.[15,16] Several studied have reported that PD-L1/PD-1 is expressed in BTC tumor cells and tumor-infiltrating leukocytes.[17-19] Higher PD-L1 expression in tumors was associated with poor prognosis. These studies provided a rationale for PD1/PD-L1 inhibitor immunotherapy in BTC patients.

The effectiveness of PD-1/PD-L1 inhibitors in BTC treatment remains controversial. Previous studies have provided initial assessment of nivolumab and pembrolizumab by combination chemotherapy or monotherapy in patients with advanced BTC.[20-25] Moreover, even less information has been reported in PD-1/PD-L1 inhibitor clinical trials in BTC patients. Although more clinical efforts have focused on combined ICIs for chemotherapy, ICI monotherapy is still an option for patients intolerant to traditional chemotherapy. Clinical studies should be conducted to obtain more evidence for ICI monotherapy. The present study introduced the effects of anti-PD-1 antibody camrelizumab in patients with recurrent ICC to evaluate its safety and efficacy. In addition, available literature was reviewed to elucidate the role of ICIs in BTC treatment.

Methods

Patient Characteristics

Retrospective data were collected from May 10, 2019 to December 3, 2019 at the First Affiliated Hospital, School of Medicine, Zhejiang University. Four patients with unresectable or postoperative recurrence BTC confirmed histologically or cytologically were enrolled in the study (Figure 1). One case

Table 1. Patients Baseline Disease Characteristics.

Characteristic	1	2	3	4
Age	56	58	60	52
Sex	Male	Male	Female	Female
Primary tumor site	Intrahepatic bile duct	Intrahepatic bile duct	Gallbladder	Common bile duct
ECOG performance status	1	0	0	1
Histological grade	Moderate-poor differentiated	Moderate	Poor	Moderate
Recurrent or metastatic site	Lung and liver	Bone	Liver	Liver
Treatment related Adverse event			Skin rash grade3	
Tumor response to treatment	Partial response			

Table 2. Tumor Response to Treatment.

	Anti-PD-1 treatment (n = 4)	PFS
Partial response	1 (25%)	4.9 months
Progressive disease	3 (75%)	

had recurrent ICC with liver and lung metastases post operation, 1 case had recurrent ICC with bone metastasis post operation, and 2 cases were diagnosed with gallbladder cancer with liver metastasis and unresectable extrahepatic bile duct cancer, respectively. The recurrent patients underwent surgery in October and July 2018, respectively. Unfortunately, progressive disease was observed after chemotherapy combining cisplatin with gemcitabine. New lung and liver metastases were discovered in the patient. Another patient was found to have multiple bone metastases. Both of these patients received PD-1 inhibitor monotherapy and refused the continued chemotherapy. The other 2 cases with unresectable BTC were intolerant to the serious adverse effects of chemotherapy and received anti-PD-1 monotherapy. Intravenous camrelizumab (SHR-1210; Jiangsu Hengrui Medicine Co. Ltd, China) was subsequently administered at a dose of 3 mg/kg 3 weeks until disease progression or unacceptable toxicity were observed. SHR-1210 is a selective, humanized, high-affinity immunoglobulin G4-kappa monoclonal antibody against PD-1. Informed consent was obtained from all patients. Patient baseline disease characteristics are summarized in Table 1.

Patients were followed up regularly to monitor the adverse events and treatment responses. Blood tests were performed for complete blood count, renal and liver function, tumor markers, and coagulation studies. Tumor response was assessed using computed tomography (CT) or magnetic resonance imaging (MRI) every 4 weeks until treatment discontinuation according to response evaluation criteria in solid tumor (RECIST) version 1.1.[26] Objective response was defined as complete or partial response. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[27]

Gene sequencing analysis was performed to identify the patients for therapeutic efficiency (Illumina Hiseq). Tumor tissues or blood samples for PD-L1 expression, microsatellite instability (MSI), tumor mutation burden (TMB), and DNA mismatch repair deficiency (dMMR) analysis were collected from patients. PD-L1-positive expression was defined as 1% or greater of tumor or tumor-associated immune cells.

Results

Efficacy

According to the resulting data, one out of 4 patients had a positive response (Table 2), with a PFS of 4.9 months. This recurrent ICC patient had a partial response and the time to response was 2 months after treatment. The lung and liver metastases were well-controlled after 3 cycles of therapy as assessed by CT scans. CT examination showed that lung and liver metastases continued to decrease (Figures 2 and 3), and the patient had a partial response (PR) according to the standard RECIST 1.1 criteria, which lasted up to 4.9 months. Unfortunately, the patient experienced upper gastrointestinal bleeding due to ulcer 6.9 months from the beginning date of treatment, gave up operation therapy, and died on November 29, 2019. Another recurrent ICC case with bone metastases and gallbladder cancer with liver metastasis experienced disease progression during treatment, at which point the therapy was discontinued. The unresectable extrahepatic bile duct cancer patient stopped the treatment after developing grade 3 rash. Gene sequencing analysis showed that none of the patients had high-level MSI and PD-L1 expression and no dMMR-related genes were detected. In addition, the 4 patients' TMB values were 0.7, 2.3, 2.0, and 1.5 muts/Mb, respectively.

Safety

No treatment-related deaths occurred during the treatment process. The unresectable gallbladder cancer patient developed grade 3 skin rash after 2 weeks of treatment, received glucocorticoid treatment, and discontinued the therapy. Furthermore, fever, bone marrow suppression, hand-foot syndrome, amylase increase, hypertension, alopecia, diarrhea, pleurisy, pneumonitis, or any other adverse events did not occur.

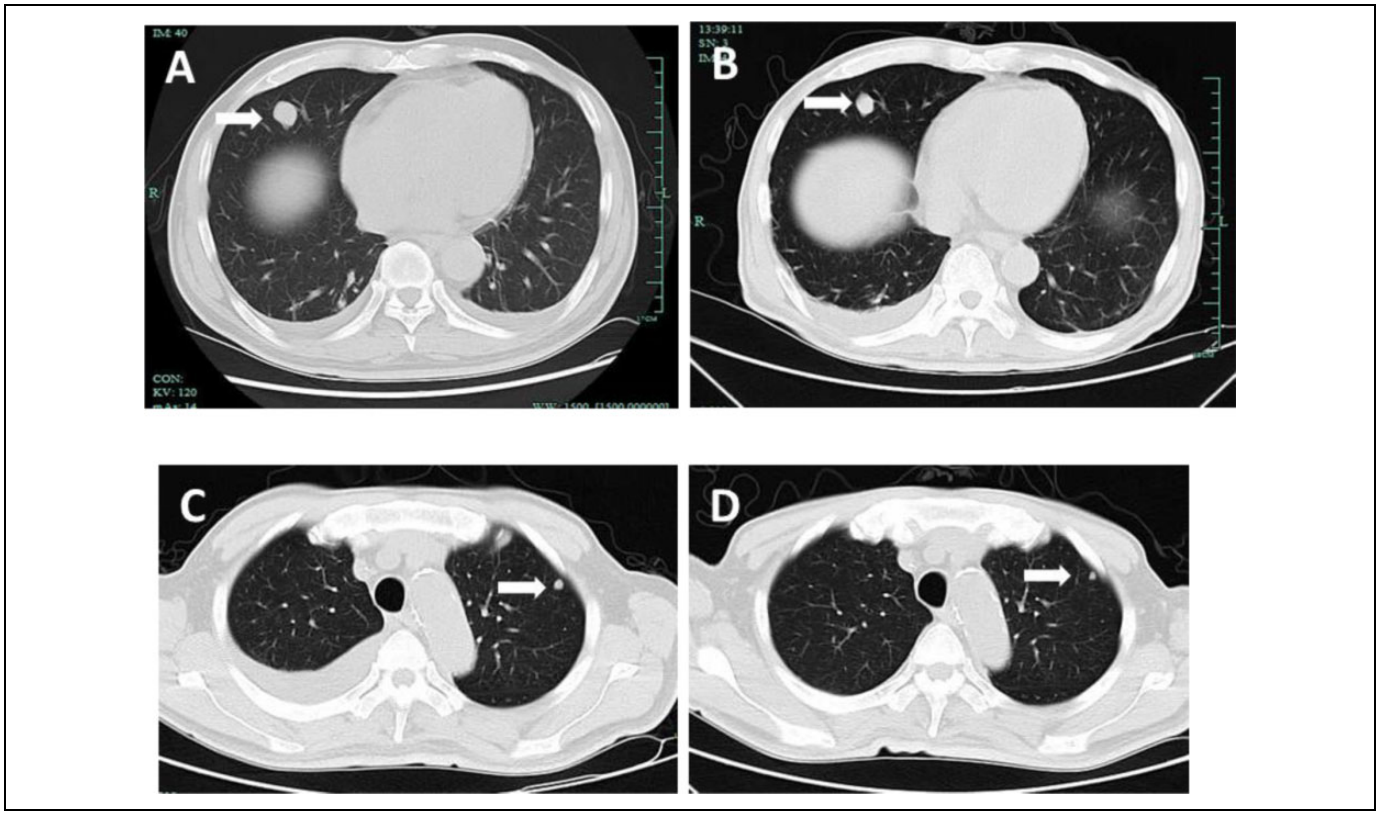

Figure 2. CT images demonstrate the significant reduction in size of lung metastases after treatment. A and C: lung metastases before treatment; B and D: lung metastases after treatment.

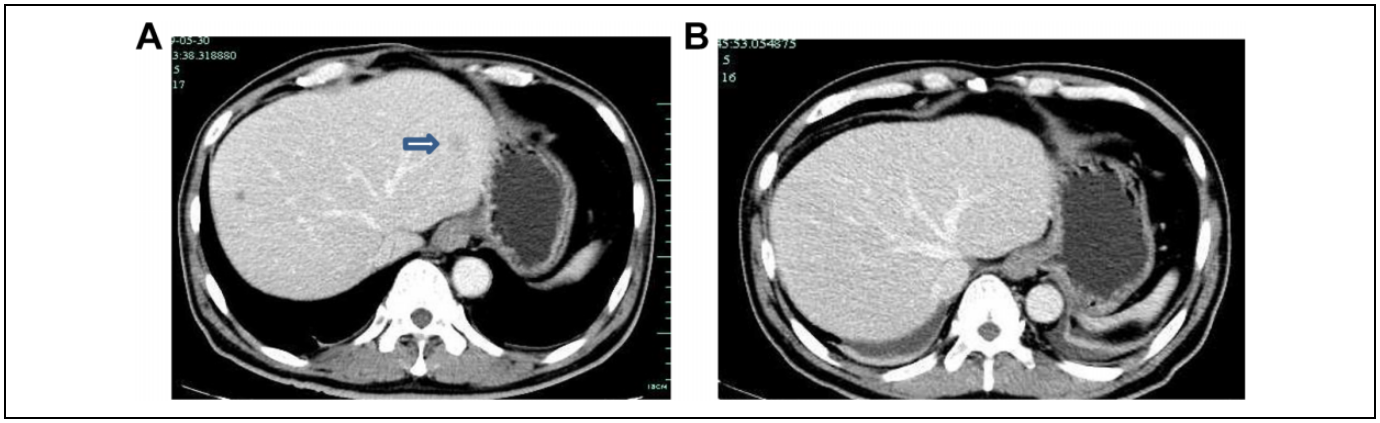

Figure 3. CT images liver metastases achieved complete remission after treatment. A: liver metastases before treatment; B: liver metastases after treatment.

Discussion

PD-1 has been demonstrated to have efficacy in solid tumors.[28-31] Although investigation of its utility has been focused on combination of ICIs with chemotherapy, ICI monotherapy still had a response in 10–35% of patients.[32] Monotherapy is suitable for BTC patients with failed gemcitabine-cisplatin chemotherapy or those intolerant to traditional chemotherapeutic regimens.

The present study evaluated the efficacy and safety of anti-PD-1 camrelizumab monotherapy in 4 cases of advanced BTC. One out of 4 patients had a partial clinical response without any unexpected safety issues. Furthermore, the data showed that higher TMB, dMMR, MSI-H, and PD-L1 expression is not able to distinguish among patients who might benefit from single immunotherapy. In addition, literature on treatment of BTC patients with anti-PD-1 inhibitors was comprehensively summarized.

The efficacy of PD-1 blockers for patients with BTC has been supported by several clinical trials before, and the combination with chemotherapy achieved more encouraging

clinical outcomes than monotherapy. Sun et al have reported that anti-PD-1 (pembrolizumab and nivolumab) and combined chemotherapy might lead to a longer overall response (OR), PFS, higher ORR, and disease control rate (DCR) than a single administration in Chinese patients with BTC. Anti-PD-1 plus chemotherapy in 38 patients had a treatment response of 34.25%. The median PFS and OS were 5.1 months and 14.9 months, respectively.[20] Recently, a multi-center, open-label, phase I clinical trial on nivolumab alone or combination therapy in BTC was conducted in Japan. Only 1 out of 30 patients had an OR in the nivolumab alone group. However, 11 out of 30 chemotherapy-naïve patients had an OR in the nivolumab combined with cisplatin and gemcitabine group.[21] Furthermore, Sui et al has reported that 2 patients with relapsed ICC treated with pembrolizumab combined with chemotherapy achieved a complete response (CR) and survived for longer than 16 and 13 months, respectively. They also found a correlation between a high indel ratio and immunotherapy response in ICC patients.[33] Mou et al have reported that a combined administration of pembrolizumab, oxaliplatin, and tegafur demonstrated a good response in a metastatic ICC patient after surgery with metastatic lesions in complete remission.[34]

The present study also assessed the safety and efficacy of combining an antiangiogenic agent with ramucirumab and pembrolizumab in BTC patients with failed gemcitabine-cisplatin chemotherapy.[35] Twenty six patients received a simultaneous inhibition treatment of vascular endothelial growth factor receptor 2 and PD-1. The resulting objective response rate was only 4%. Median PFS and OS were 1.6 months and 6.4 months, respectively. No difference was observed in median PFS between patients with positive/negative PD-L1 expression (1.5 and 1.6 months). Patients with positive PD-L1 expression had increased OS compared to patients with negative PD-L1 expression. Furthermore, nivolumab-based immunotherapy combined with lenvatinibin was also introduced in the ICC patient.[36] The patient developed a recurrent tumor 5 months after surgery, although cisplatin and xeloda were administered. The patient was then simultaneously administered nivolumab and lenvatinib. MRI and CT showed a PR after 9 months of therapy, and liver metastases became smaller and almost disappeared.

In addition, the efficacy of PD-1 monotherapy has also been assessed in BTC and the results are controversial. In a non-randomized phase I study, no patient had a complete response and only 3% achieved a partial response with nivolumab alone.[21] In a phase II study, the results showed that the effectiveness of nivolumab monotherapy in patients with advanced BTC, percentage of patients with PR and stable disease (SD) was 17% and 38% respectively, and there was an overall DCR of 55%.[24] In another phase 2 KEYNOTE-158 study, pembrolizumab monotherapy achieved a response in 6% of patients.[23] Bang et al have also reported that 17% of evaluable BTC patients with PD-L1 expression of 1% or greater responded to pembrolizumab monotherapy in the KEYNOTE-028 basket trial.[22] Phase II clinical trial data demonstrated a higher OR rate than phase I clinical trial data. However, other results showed no or low response to nivolumab monotherapy in BTC.[20,21] This might be attributed to a lower proportion of patients who experienced failure with multiple lines of therapy. Furthermore, phase I trial emphasized safety rather than efficacy. Based on BTC patients in our center, the efficiency of a single anti-PD-1 antibody camrelizumab administration for treatment of patients with refractory BTC was reported. Camrelizumab showed promising antitumor activity and a manageable toxicity profile in tumors.[37-39] The present study demonstrated a good response to camrelizumab monotherapy. One in 4 cases (25%) experienced a reduction in lung metastasis size. One case experienced a decrement of SD and CA-199 level bone metastasis after surgery. Resistance to gemcitabine-cisplatin chemotherapy was the common characteristic in these 2 cases. These results are consistent with a previous study that also found nivolumab monotherapy to be associated with antitumour activity in BTC patients.[21]

It is difficult to accurately screen out the patients who might have that clinical benefits presented by extended survival. Several biomarkers, including PD-L1 expression, high MSI, dMMR, and high TMB have been approved by the Food and Drug Administration for immunotherapy.[40] PD-L1 expression in tumor or tumor-associated immune cells has been associated with increased clinical benefits from PD-1 or PD-L1 blockade therapy in some tumors. In the KEYNOTE-028 trial, PD-1-positive patient OS was obviously better than that in PD-1-negative patients.[22] Umemoto et al found that CD8+ T cells expressing PD-1 near tumor cells are associated with PD-1 therapy response in BTC.[41] MMR deficiency and TMB have also been demonstrated as important predictive biomarkers for immunotherapy.[42-44] However, the expression of these biomarkers may be affected by various factors, including time fluctuations and tumor heterogeneity. These results were based on small sample sizes and the opposite findings were also reported in other studies. The KEYNOTE-158 study published an ORR of 6.6% in patients with a combined PD-L1 score (CPS) $\geq$1. Patients with low PD-L1 expression (<1%) were also responded to Nivolumab therapy, and there was no association between PD-L1 expression and a clinical response in the KEYNOTE-189 and KEYNOTE-407 trials.[30] In the trial investigating combined administration of pembrolizumab and ramucirumab in advanced BTC, only 1 patient achieved an OR in PD-L1-positive patients.[35] Previous cases also showed that PD-L1 expression, high TMB, and MSI-H cannot completely characterize patients who will benefit from immunotherapy.[33] The present data suggested that none of the patients had high PD-L1 expression, MSI, dMMR, or TMB. This might be due to the proportion of patients with relatively low MSI-H. Previously published results have indicated that the incidence of MSI-H is <10% in ampullary cancer and ICC and approximately 5% or lower in GBC and extrahepatic cholangiocarcinoma.[15,31] Of the PD-L1-positive BTC patients enrolled in the KEYNOTE-028 study, 17% had positive responses to pembrolizumab monotherapy.[16]

The present study determined the potential positive effects of camrelizumab on treatment of Chinese patients with

refractory BTC. However, the reliability of these efficiency data needs further external validation due to a relatively low sample size in the present study.

Treatment safety is another major issue for the oncology community. Immune-related adverse event (IRAE) occurrence is thought to unbalance the immune system via activated T-cells.[45,46] Previous published data have indicated that most IRAEs were mild and manageable. A meta-analysis including 12,808 cancer patients reported that the overall incidence of IRAE was 26.82% and 6.1% in severe grade patients treated with PD-1/PD-L1 inhibitors. The incidence of IRAE was 18.5% in patients with pembrolizumab and 16.67% in the atezolizumab group, which was lower than the incidence in patients treated with nivolumab. The incidence of severe grade IRAE ranged from 5 to 8% (8.25% with nivolumab, 5.1% with pembrolizumab, and 5.28% with atezolizumab).[47] IRAE can occur in almost all organs, including dermatologic, gastrointestinal, hepatic, endocrine, respiratory, and musculoskeletal systems, which are most frequently affected by ICIs. The most common IRAE in anti-PD-1 therapy include fatigue, pruritus, rash, vitiligo, diarrhea, hypothyroidism, pneumonitis, hepatitis, and nephritis. In the present study, 1 patient experienced a skin rash (grade 3) and was treated by glucocorticoid treatment, after which the therapy was discontinued.

In conclusion, the present data provided clinical evidence that PD-1 inhibitor camrelizumab monotherapy might have antitumor activity in patients with advanced BTC. Although data validity and reliability is limited due to small sample size and short follow-up duration, these findings still provide valuable clues for a further exploration in patients who are intolerant or insensitive to traditional chemotherapy.

Authors' Note

This study was approved by IRB of First affiliated hospital of Zhejiang University (IIT20200242A). All procedure obtained the consent from patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Shusen Zheng https://orcid.org/0000-0003-1459-8261

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