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PD-1 inhibitor combined with chemotherapy or lenvatinib in advanced gallbladder cancer: a retrospective comparative study

Hong-yan Ma[1], Qin-wen Tai[2] and Hao Song[2*]

Abstract

Background Gallbladder cancer (GBC) is a refractory primary cancer. Some GBC patients are prone to recurrence even after surgical resection. In such cases, chemotherapy is the most common non-surgical treatment. The emergence of programmed cell death protein 1 (PD-1) inhibitors and targeted therapy have provided an additional option for those suffering from advanced tumors.

Methods This was a retrospective study involving patients with advanced GBC treated at the Shanghai Eastern Hepatobiliary Surgery Hospital between June 2019 and June 2022. The patients who received a PD-1 inhibitor (tislelizumab) with chemotherapy or with lenvatinib were retrospectively analyzed. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) was used as the efficacy evaluation standard. The overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and tumor marker CA199 were evaluated.

Results This study involved 61 patients with advanced GBC. Of these, 32 patients received tislelizumab and GS (gemcitabine and TS-1) chemotherapy, whereas 29 patients received tislelizumab and lenvatinib. For the Tislelizumab plus GS chemotherapy group, the median OS and PFS were 19.64 ± 11.81 (95% CI: 16.47–25.20) and 15.44 ± 13.42 (95% CI: 12.08–22.25) months, respectively. For the lenvatinib group, the OS and PFS were 13.06 ± 9.41 (95% CI: 9.72–16.63) and 10.34 ± 10.03 (95% CI: 6.56–14.13) months, respectively. The ORR and DCR were 59.38% and 81.3%, respectively, for the Tislelizumab plus GS chemotherapy group, which were significantly longer than those for the Tislelizumab plus Lenvatinib group. Treatment-related adverse events were similar between the groups.

Conclusion Tislelizumab combined with GS chemotherapy provides a safe and more efficient treatment option for advanced GBC patients.

Keywords Gallbladder cancer, PD-1 inhibitors, Chemotherapy, Lenvatinib, Retrospective study

Introduction

Gallbladder cancer (GBC) is a highly malignant tumor that metastasizes at distant sites through hepatoduodenal ligament lymph nodes [1, 2]. Surgical resection is the only treatment for curing GBC; however, approximately 60% of cases are not eligible for surgery and are insensitive to conventional chemotherapy [3]. According to previous reports, the objective response rate (ORR) of chemotherapy is currently only 26%, with a median survival time of only 11.7 months [4]. Programmed cell death protein 1 (PD-1) inhibitors and targeted drugs exert significant

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therapeutic effects on malignant tumors. However, regarding the treatment of GBC, few clinical reports have explored whether it is better to combine PD-1 inhibitors with chemotherapy or targeted drugs [5].

Methods

Patients

In this study, 83 GBC patients treated at the Shanghai Eastern Hepatobiliary Surgery Hospital between June 2019 and June 2022 were retrospectively screened. 12 patients did not sign the informed consent form for the clinical trial and 10 patients were lost to follow-up after one course of treatment (Fig. 1). Finally, this study comprised 61 patients, with 32 receiving tislelizumab and GS (gemcitabine and TS-1) chemotherapy and 29 receiving tislelizumab and lenvatinib. All patients had a PS score below 2 and could take care of themselves (Table 1). The study was approved by the Institutional Review Board and Ethics Committee of the Southern Medical University Shenzhen Hospital(No.2022KTSCX021). This research was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) GBC confirmed by pathology; (2) tumor stage III or IV according to TNM staging; (3) no radiotherapy or targeted therapy; (4) voluntary participation in long-term follow-up; (5) PS score < 2; (6) ineligibility for radical surgical resection or recurrence after surgery; and (7) at least one measurable lesion prior to treatment initiation.

The exclusion criteria were as follows: (1) undiagnosed GBC; (2) other concurrent tumors; (3) concurrent insufficiency of major organs; or (4) severe mental disorders and no complete evaluation at the time of data collection.

Patient evaluations and adverse events

Based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [6], the tumor response was rated as complete remission (CR), partial remission (PR), stable disease (SD), or disease progression. The ORR included CR and PR cases, while the disease control rate (DCR) included CR, PR, and SD cases. Both progression-free survival (PFS) and overall survival (OS) were evaluated. PFS referred to the time from the patient receiving immunotherapy to the first occurrence of disease progression or death from any cause. Adverse events were judged according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [7]. Safety was continuously evaluated every three weeks through laboratory tests, including blood routine tests, liver function tests, thyroid function tests, myocardial enzyme tests, and chest X-rays.

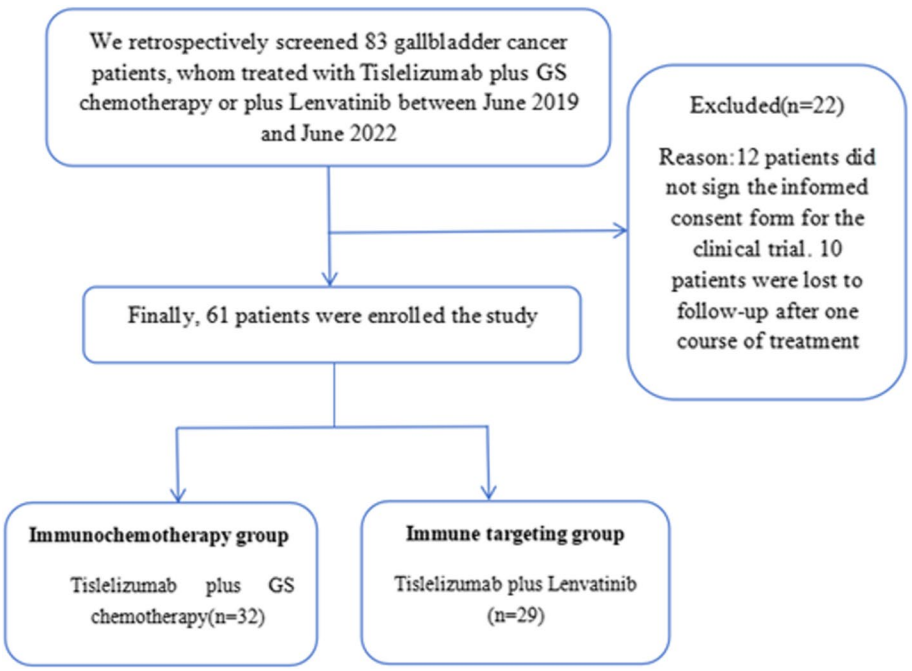

Fig. 1 Flow diagram of the study. ✱A total of 61 people were included in this study. 32 people were treated with tislelizumab and GS. chemotherapy. 29 people using tislelizumab and lenvatinib

Table 1 Baseline characteristics

Characteristic	Tislelizumab plus GS chemotherapy ($n=32$)	Tislelizumab plus Lenvatinib ($n=29$)	*P* value
Age (n, %)			0.120
≥60	17(53.1%)	19(65.5%)	
<60	15(46.9%)	10(34.5%)	
Sex (n, %)			0.054
Male	20(62.5%)	10(34.5%)	
Female	12(37.5%)	19(65.5%)	
Hepatitis Virus infection(n, %)			0.841
Yes	6(18.7%)	7(24.1%)	
No	26(81.3%)	22(75.9%)	
Smoking history(n, %)			0.883
Yes	16(50%)	16(55.2%)	
No	16(50%)	13(44.8%)	
Gall stone disease (n, %)			0.972
Yes	20(62.5%)	18(62.9%)	
No	12(37.5%)	11(37.1%)	
Obstructive jaundice(n, %)			0.768
Yes	11(34.4%)	8(27.6%)	
No	21(65.6%)	21(72.4%)	
Performance status(n, %)			0.736
0–1	25(78.1%)	24(82.8%)	
2	7(21.9%)	5(17.2%)	
Previous surgery(n, %)			0.249
Yes	24(75%)	26(89.7%)	
No	8(25%)	3(10.3%)	

Treatment

Of the 61 patients, 32 received a PD-1 inhibitor (tislelizumab) and GS chemotherapy, while 29 received tislelizumab and lenvatinib. All patients signed an informed consent form before treatment. Tislelizumab was administered at 200 mg on the first day, on a three-week medication cycle. Gemcitabine was administered at 1000 mg per square meter of body surface area on the second day. TS-1 was administered at 40 mg orally twice a day for two consecutive weeks and discontinued for one week. Gemcitabine was administered again on the eighth day. After eight courses of treatment, gemcitabine was discontinued, and oral TS-1 was continued. Tislelizumab was continued for all three weeks. All patients received at least two cycles of treatment. Lenvatinib was administered orally at a dose of 12 mg for patients with a body weight ≥ 60 kg and at a dose of 8 mg for patients with a body weight < 60 kg once a day. All these drugs should be used on time until intolerable side effects or disease progression occurs.

All patients underwent routine blood tests, serum tumor marker analyses, and imaging tests such as CT. Imaging studies were used to assess the treatment effect after at least three cycles of treatment, and adverse events were recorded.

Follow-up

The follow-up was performed via case reviews, telephone calls, and follow-up visits. The follow-up started on the date of the first immunotherapy session and ended at the time of the last follow-up. The follow-up deadline was 30 June 2022.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range) according to distribution. Categorical variables were analyzed using the chi-square test and Fisher's exact test, and continuous variables were analyzed using the independent samples t-test. Survival analyses were performed using the Kaplan–Meier method. A significant threshold was set at a value of $p < 0.05$. All analyses used SPSS (V.23.0, Chicago, Illinois, USA).

Results

General findings

Between June 2019 and June 2022, 61 patients who met the eligibility criteria were categorized into two treatment cohorts: 32 in the Tislelizumab plus GS chemotherapy group and 29 in the Tislelizumab plus Lenvatinib group. The baseline patient characteristics are reported in Table 1. There were 36 patients over the age of 60, accounting for 51.3% and 65.5% of the Tislelizumab plus GS chemotherapy group and the Tislelizumab plus Lenvatinib group, respectively. The groups had 30 males in total, accounting for approximately 50%. Only 13 people had been infected with the hepatitis virus in the past. Furthermore, 38 patients had gallstones, accounting for 68.7% of all cases. All patients had ECOG scores below 2. Most patients had a normal BMI. The two groups did not exhibit any significant differences regarding prior surgery. The PFS and OS in the subgroup analyses are presented in Fig. 2. Furthermore, there was no significant difference in TMB values or common mutated genes between the two groups. The most mutated genes included TP53, CDKN2A, ARID1A, SMAD4, and ERBB2 (Fig. 3).

Efficacy and prognosis analysis

By the end of June 2022, 21 deaths and 23 deaths had occurred in the chemotherapy group and the lenvatinib group, respectively. The median OS was 17.8 months (95% CI: 13.73–22.07) in the chemotherapy group, which was longer than that in the lenvatinib group (12.5 months, 95% CI: 10.6–14.3). The median PFS was 12.1 months in the chemotherapy group, which was significantly longer than that in the lenvatinib group (5.1 months, 95% CI: 3.59–6.61) (Fig. 3). At the end of the study, seven patients in the Tislelizumab plus GS chemotherapy group and three patients in the Tislelizumab plus Lenvatinib group were alive (Fig. 4). Nine patients in both groups showed complete remission, including six in the chemotherapy group and three in the Tislelizumab plus Lenvatinib group. Twenty-seven patients showed partial remission of tumors to varying degrees, including 19 in the chemotherapy group and eight in the lenvatinib group (Table 2). The DCR and ORR were 71.9% and 59.38%, respectively, in the chemotherapy group and 55.2% and 31.03%, respectively, in the lenvatinib group (Fig. 5). Some patients' tumors were significantly reduced on CT. Measured according to RECIST 1.1, the tumors shrunk by over 30%, reaching a partial reaction(PR) degree. After treatment, we found that both groups of patients had partial relief. Compared to before treatment, some patients' tumor diameters have reduced by 30%, meeting the criteria for PR. There was also one case of lung metastasis. After treatment, the tumor shrank significantly and partially disappeared (Fig. 6). Furthermore, there was a significant difference in CA19-9 levels between the two groups. After three months of treatment, the CA19-9 values of the chemotherapy group patients generally decreased and were significantly lower than those of the Tislelizumab plus Lenvatinib group patients (Table 3).

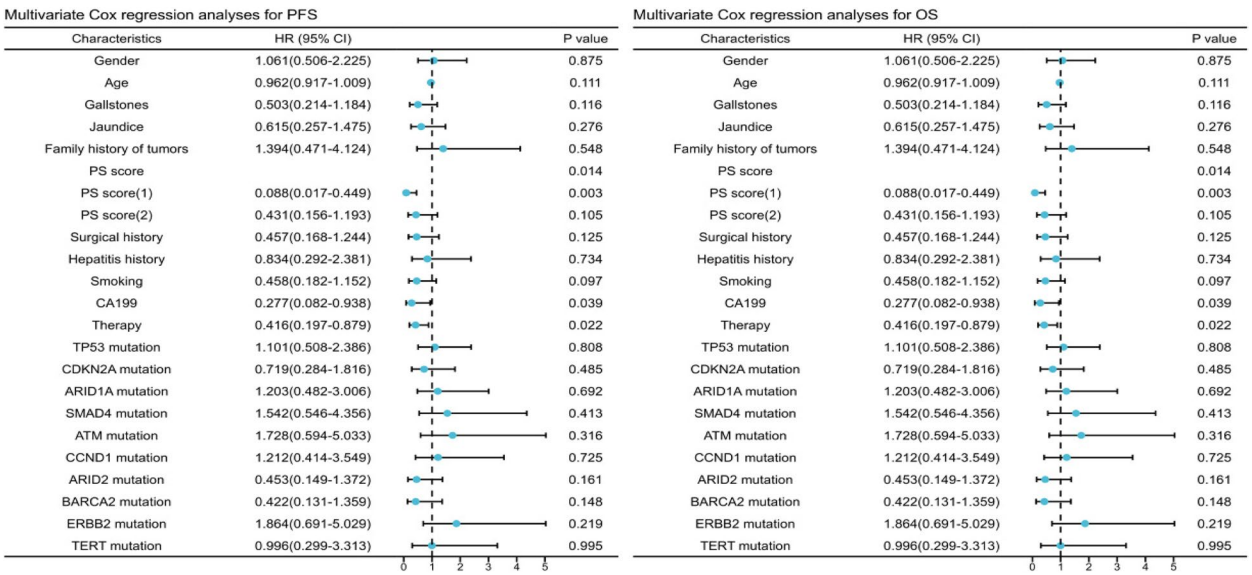

Fig. 2 Subgroup analyses of progression-free survival (PFS) and overall survival (OS) in the entire cohort. ✱We used COX regression analysis to examine the impact of basic conditions on FPS and OS in two groups of patients. we found that there was no significant difference in the pre-treatment conditions between the two groups of patients

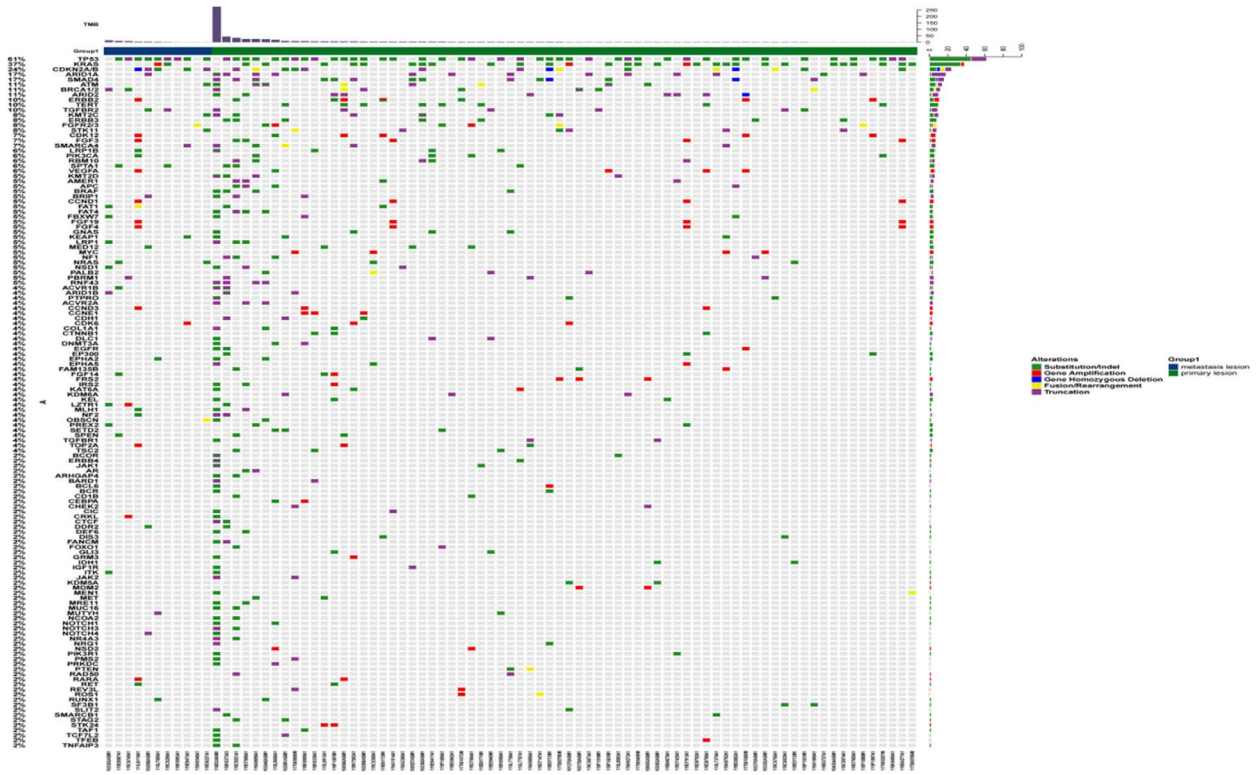

Fig. 3 Gallbladder cancer mutation gene heatmap

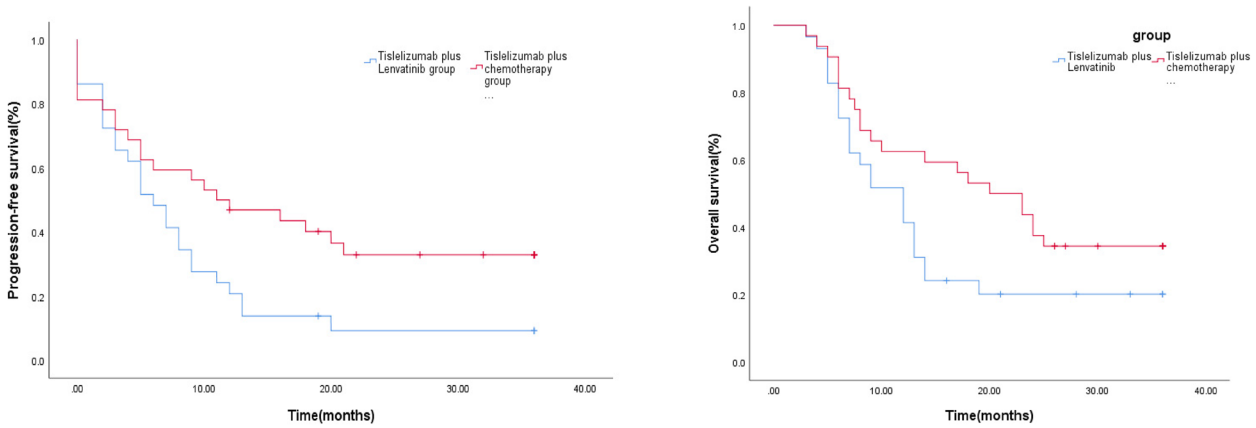

Fig. 4 The progression-free survival and overall survival Kaplan–Meier analyses. ✱Through Kaplan–Meier analyses, the FPS and OS of patients in tislelizumab and GS. chemotherapy were higher than combination with lenvatinib, $p < 0.05$

Adverse events

Treatment-related adverse events (TRAEs) were 84.37% (27/32) and 89.65% (26/29) in the Tislelizumab plus GS chemotherapy group and the Tislelizumab plus Lenvatinib group, respectively (Table 4). The incidence of TRAEs were similar in the two groups. No drug-related deaths occurred in either group. The most common side effects in the Tislelizumab plus GS chemotherapy group were nausea, vomiting, fatigue, and reduced granulocytes, while patients in the Tislelizumab plus Lenvatinib group were more likely to exhibit rashes and oral ulcers. Regarding other drug side effects, no significant difference was observed between the two groups (Fig. 7).

Table 2 Tumor response to treatment

	Tislelizumab plus GS chemotherapy($n=32$)	Tislelizumab plus Lenvatinib($n=29$)	*P* value
PFS(month)	14.09 ± 12.76	8.2 ± 9.31	0.046
OS(month)	19.14 ± 11.45	12.72 ± 9.5	0.021
Overall response(n, %)			
DCR	23(71.9%)	16(55.2%)	0.276
ORR	19(59.38%)	9(31.03%)	0.027
CR	6(18.8%)	3(10/3%)	0.355
PR	19(59.4%)	8(27.6%)	0.013
SD	23(71.9)	16(55.2%)	0.276
PD	10(31.3%)	12(41.4%)	0.411

Discussion

GBC has a high malignancy and poor prognosis. Radical surgery is the only possible cure. However, as early diagnosis is difficult, most cases are at an advanced or late disease stage at the first diagnosis. Consequently, radical surgery is not an option, and the disease requires comprehensive treatment, including chemotherapy, radiotherapy, targeted therapy, immunotherapy, and supportive treatment. In recent years, non-surgical treatment for GBC has not made much progress [8]. Targeted therapies have made important inroads in the treatment of BTC, with the approval of FGFR inhibitors and the IDH1 inhibitor. But there is no approved targeted drug

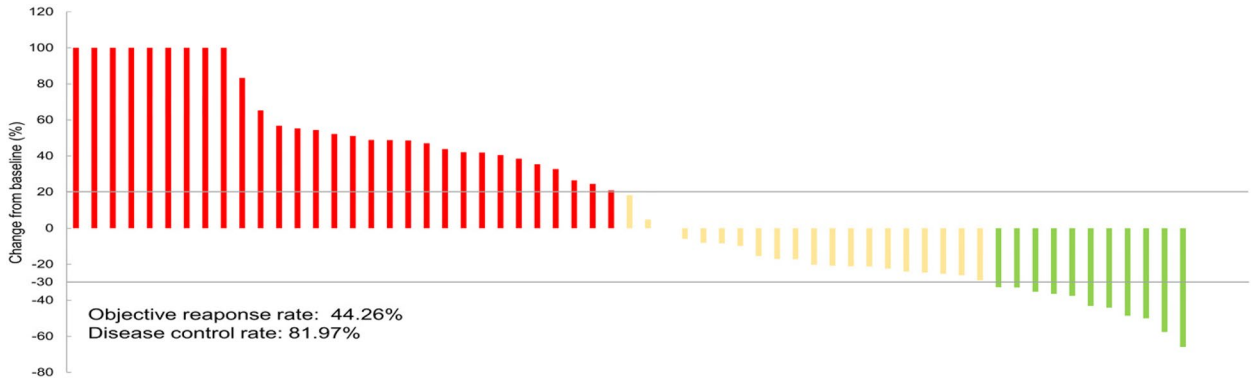

Fig. 5 Maximum percentage change in the sum of the diameters of the target lesions from Baseline(Red represents disease progression(PD); Orange represents disease stability(SD); Green represents partial or complete remission(PR or CR))

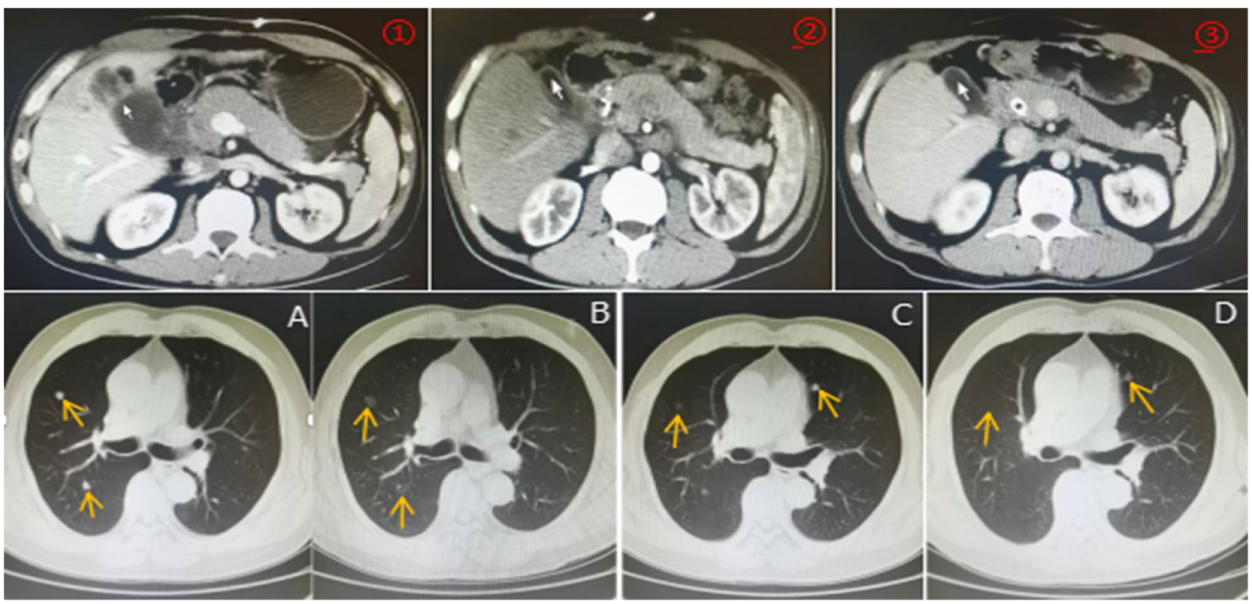

Fig. 6 The image is a CT scan of a patient with advanced GBC. ①CT scans before treatment, ②3 months after treatment, ③6 months after treatment. The following figure shows a patient with lung metastasis from GBC, A and C are before treatment; B and D are images after treatment

Table 3 CA19-9 changes in two groups

Blood test time	Tislelizumab plus GS chemotherapy($n=32$)	Tislelizumab plus Lenvatinib($n=29$)	*P* value
Before treatment	343.69 ± 291.41	293.63 ± 311.57	0.475
3 months later	137.56 ± 179.12	297.55 ± 310.22	0.042
6 months later	118.32 ± 153.45	283.52 ± 306.45	0.034
12 months later	78.11 ± 187.90	294.89 ± 358.41	0.020

for GBC in China [9]. However, the rapid development of immunotherapy, especially the emergence of ICIS, has considerable potential for the treatment of GBC. ICIS has been successfully used in the treatment of various solid tumors, including malignant melanoma and lung cancer, but its application in GBC is still in the exploratory stage [10]. PD-L1 has been reported to be strongly related to the response to PD-1 inhibitors in several tumors [11], and its predictive value in GBC should be further validated. Chemotherapy is the fundamental element in treating advanced GBC. Cancer chemotherapy is viewed as a method that mainly affects tumor cells, but increasing evidence indicates that cytotoxic drugs also affect the immune system and T cells [12]. At present, the treatment of unresectable GBC mostly adopts PD-1 or PD-L1 combined with targeted therapy or chemotherapy. The treatment plan that is better in terms of efficacy still needs to be confirmed in clinical practice. Many tumors are treated with immunotherapy combined with targeted drugs or chemotherapy. Some studies tested immunotherapy in combination with gemcitabine-based chemotherapy as a first line treatment. To treat GBC and BTCs with advanced and metastatic settings, these studies showed promising results, with ORR of 31–63% [13]. There are also clinical studies showing that the combination of immunotherapy with Lenvatinib has a good effect in the treatment of cholangiocarcinoma, some cases showing partly remission [14]. Although there are many similar studies, there are few clinical reports on which is better between chemotherapy and targeted drug for gallbladder cancer in most patients. A clinical study [15] examined the effects of immune combination chemotherapy in 1,069 patients with biliary tract cancer. These patients were randomly assigned to receive either pembrolizumab combined with gemcitabine and cisplatin ($n=533$) or a placebo combined with gemcitabine and cisplatin ($n=536$). The median follow-up period was 25.6 months (IQR 21.7–30.4). The median overall survival in the pembrolizumab group was 12.7 months (95% CI 11.5–13.6), compared to 10.9 months in the placebo group. Resulting in a hazard ratio of 0.83 (95% CI 0.72–0.95) with a p-value of 0.0034. This study demonstrates the beneficial role of immunotherapy in treating biliary tract cancer. However, gallbladder cancer has a markedly different pathogenesis compared to intrahepatic cholangiocarcinoma. In this research, we used Tarelizumab in combination with gemcitabine and TS-1 to treat gallbladder cancer.

We chose to replace cisplatin with TS-1 want to mitigate the potential adverse effects of strong chemotherapy drugs, which could compromise the patients' immune function and thus impact the efficacy of Tarelizumab. We aimed to reduce side effects and enhance the effectiveness of the immunotherapy and ultimately achieving promising outcomes. This study evaluated the efficacy and safety of tislelizumab combined with GS chemotherapy and tislelizumab combined with lenvatinib in advanced GBC patients. For a comparative study, 61 patients with unresectable GBC were divided into two groups. The addition of tislelizumab to chemotherapy significantly

Table 4 Treatment-related adverse events

Adverse events(n, %)	Tislelizumab plus GS chemotherapy($n=32$)	Tislelizumab plus Lenvatinib($n=29$)	*P* value
Fever	10(31.3%)	5(17.2%)	0.331
Celialgia and Diarrhea	9(28.1%)	6(20.7%)	0.501
Fatigue	15(46.9%)	6(20.7%)	0.032
Skin rash	6(18.8%)	9(31%)	0.266
Nausea and Omitting	26(81.3%)	16(55.2%)	0.028
Leukopenia	17(53.1%)	7(24.1%)	0.021
Hypothyreosis	3(9.4%)	4(13.8%)	0.589
Myocarditis	1(3.1%)	3(10.3%)	0.255
ALT or AST elevation	7(21.9%)	5(17.2%)	0.649
Hypertension	5(15.6%)	8(27.6%)	0.255
Hand foot syndrome	4(12.5)	5(17.2%)	0.602
Pneumonia	1(3.1%)	2(7.1%)	0.476
Oral ulcer	8(25%)	12(41.4%)	0.174

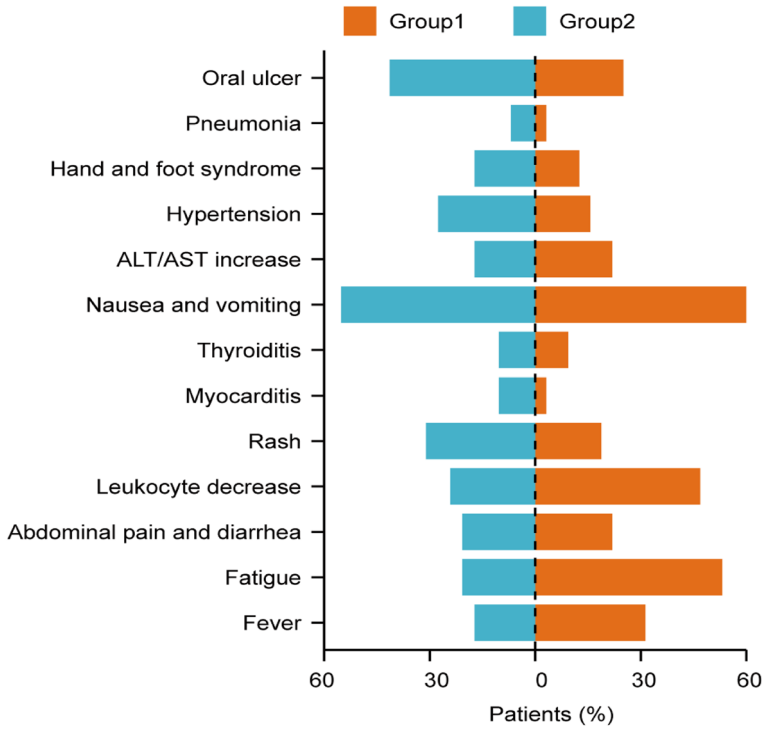

Fig. 7 Frequency of drug side effects in two groups of patients(Group 1: Tislelizumab plus chemotherapy; Group 2: Tislelizumab plus Lenvatinib)

extended the survival time and improved the proportion of patients who achieved an objective response. The OS period of the chemotherapy group patients was significantly longer than that of the lenvatinib group patients. Chemotherapy could also affect the tumor microenvironment and promote antigen expression and antitumor immune response [16]. Therefore, theoretically, immunotherapy and chemotherapy in combination could exert synergistic effects and improve survival outcomes. A previous study reported a median survival time of only 6–9 months, as well as a two-year survival rate, in patients with advanced GBC [17]. In the present study, nearly 31% of the patients survived for over two years. These findings suggest that tislelizumab combined with GS chemotherapy could significantly prolong patient survival. No statistical difference was observed in the CR rate between the two groups, but the PR rate in the chemotherapy group was significantly higher than that in the lenvatinib group. The objective remission rate was also higher in the Tislelizumab plus GS chemotherapy group.

Owing to the wide application of PD-1 inhibitors for treating tumors, immune-related adverse events (IRAEs) have attracted attention. IRAEs could occur in any organ or tissue, mainly involving the skin, the gastrointestinal tract, endocrine organs, the liver, and the lungs. Several clinical studies have reported incidence rates of 60–80% for IRAEs [18, 19]. The adverse events experienced by the patients examined in this study were mainly grades 1 or 2. The incidence of TRAEs in the Tislelizumab plus GS chemotherapy group was similar to that in the Tislelizumab plus Lenvatinib group. Thirteen drug-related side effects were observed in both groups, among which nausea, vomiting, fatigue, and granulocytopenia were more common in the chemotherapy group. However, after receiving symptomatic treatment for antiemesis, the patients' symptoms quickly improved. Before each chemotherapy session, the patients reviewed their blood routine results. If granulocytopenia was present, recombinant human granulocyte growth factor was injected subcutaneously. The most common side effects of medication, such as skin itching and maculopapules, were observed in the lenvatinib group patients, while digestive system symptoms were less common in the chemotherapy group. Due to the patients' symptoms being mild, symptomatic treatment was given, and the medication was continued. During immunotherapy, certain serious IRAEs, including pneumonia, nephritis, and myocarditis, should be closely monitored. Such adverse events, if not addressed in time, may endanger the patient's life. In this study, seven cases of grade 3 IRAEs were observed, including three pneumonia and four myocarditis cases. The symptoms improved after drug withdrawal and active treatment with glucocorticoids.

Table 5 Common mutated genes in gallbladder cancer

Mutated genes (n, %)	Tislelizumab plus GS chemotherapy($n=32$)	Tislelizumab plus Lenvatinib($n=29$)	*P* value
Expression of PD-L1	6(18.75%)	7(24.14)	0.608
TMB	12 ± 20.15	6.8 ± 7.64	0.272
TP 53	20(69%)	22(68.8%)	0.986
ERBB2	8(25%)	4(13.8%)	0.438
CDKN2A	9(28.1%)	8(27.6%)	0.963
ARID1A	7(21.9%)	9(31%)	0.417
SMAD4	8(25%)	6(20.7%)	0.689
CCND1	5(15.6%)	6(20.7%)	0.607
ATM	9(28.1%)	4(13.8%)	0.172
ARID2	5(17.2%)	5(15.6%)	0.865
BARCA	6(18.8%)	3(10.3%)	0.355
TERT	4(12.5%)	3(10.3%)	0.792

To further analyze the differences in the effectiveness of medication between the two groups, genetic testing was conducted on all patients to determine whether there were any differences in gene mutations between the two groups. Studies have reported that a high expression of PD-L1, MSI-H, and elevated TMB could predict the effect of immunotherapy in patients with GBC [20, 21]. There weresix patients in the Tislelizumab plus GS chemotherapy group and seven patients in the Tislelizumab plus Lenvatinib group were PD-L1 positive (Table 5). No significant difference was found between the two groups. However, PD-L1-positive patients, after immunotherapy, had significantly reduced tumor size and generally had a longer survival period. This indicates that the difference in treatment efficacy between the two groups is the key role played by chemotherapy drugs. Due to the small number of cases in this study, more rigorous clinical studies are needed to confirm the results.

This study was a single-center trial based on clinical practice. The findings suggest that tislelizumab could be valuable in the treatment of advanced GBC; however, its overall response rate remained low. Combining it with chemotherapy could improve the response rate. Moreover, whether such patients should be treated with immunotherapy before surgery should be assessed.

Authors' contributions

Hao Song is responsible for writing and design, Qinwen Tai are responsible for article data collection, Hongyan Ma are responsible for article data statistics and guidance.

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board and Ethics Committee of the Southern Medical University Shenzhen Hospital(No.2022KTSCX021). This research was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2. Valle JW, Kelley RK, Nervi B, et al. Biliary tract cancer. Lancet. 2021;397:428–44.
3. Ethun CG, Le N, Lopez-Aguiar AG, et al. Pathologic and Prognostic Implications of Incidental versus Nonincidental Gallbladder Cancer: A 10-Institution Study from the United States Extrahepatic Biliary Malignancy Consortium. Am Surg. 2017;83:679–86.
4. Valle JW, Borbath I, Khan SA, et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[J]. Ann Oncol. 2016;27:v28–37.
5. Piha-Paul SA, Oh DY, Ueno M, et al. Effcacy and safety of pembrolizumab or the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies. Int J Cancer. 2020;147:2190–8.
6. Schwartz LH, Seymour L, Litière S, et al. RECIST1.1 standard and disease specific adaptations: Perspectives from the RECIST working group. Eur J Cancer. 2016;62:138–45.
7. Freites-Martinez A, Santana N, Arias-Santiago S. Using the common terminology criteria for adverse events to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr. 2021;112(1):90–2.
8. Lamarca A, Hubner RA, David Ryder W, et al. Second-line chemotherapy in advanced biliary cancer: a systematic review[J]. Ann Oncol. 2014;25(12):2328–38.

9. Hyung J, Kim B, Yoo C, et al. Clinical benefit of maintenance therapy for advanced biliary tract cancer patients showing no progression after first-line gemcitabine plus cisplatin[J]. Cancer Res Treat. 2019;51(3):901–9.
10. Hsieh JJ, Chen D, Wang PI, et al. Genomic Biomarkers of a Randomized Trial Comparing First-line Everolimus and Sunitinib in Patients with Metastatic Renal Cell Carcinoma. Eur Urol. 2017;71(3):405–14.
11. Meng X, Huang Z, Teng F, Xing L, Yu J. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. Cancer Treat Rev. 2015;41:868–76.
12. Wang Z, Till B, Gao Q. Chemotherapeutic agent-mediated elimination of myeloid-derived suppressor cells. Oncoimmunology. 2017;6:e1331807.
13. Cai W, Yuan Y, Ge W. EGFR target therapy combined with GEMOX for advanced biliary tract cancers: A meta-analysis based on RCTs. J Cancer. 2018;9:1476–85.
14. Rizzo A, Frega G, Ricci AD. Anti-EGFR monoclonal antibodies in advanced biliary tract cancer: A systematic review and meta-analysis. In Vivo. 2020;34:479–88.
15. Robin Kate Kelley*, Makoto Ueno*, Changhoon Yoo. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial[J]. Lancet. 2023;401:1853–65.
16. 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 nonrandomised, multicentre, open-label, phase 1 study[J]. Lancet Gastroenterol Hepatol. 2019;4(8):611–21.
17. Li M, Zhang Z, Li X, et al. Whole-Exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the ErbB pathway. Nat Genet. 2014;46:872–6.
18. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD- L1- positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial[J]. Lancet. 2016;387(10027):1540–50.
19. Arnaud Coffin P, Maillet D, Gan HK, et al. A systematic review of adverse events in randomized trials assessingimmune check point inhibitors[J]. Int J Cancer. 2019;145(3):639–48.
20. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade[J]. Science. 2017;357(6349):409–13.
21. Ott PA, Bang YJ, Piha-Paul SA, et al. T-Cell-Inflamed Gene Expression Profile, Programmed Death Ligand 1 Expression and Tumor Mutational Burden Predict Efficacy in Patients Treated With Pembrolizumab Across 20 Cancers: KEYNOTE-028[J]. J Clin Oncol. 2019;37(4):318–27.

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