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Preliminary experience of lenvatinib, tislelizumab and transcatheter arterial chemoembolization for BCLC stage C hepatocellular carcinoma: a phase II study

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Abstract

Introduction This study evaluated the efficacy and safety of the triple combination of transcatheter arterial chemoembolization (TACE), lenvatinib, and tislelizumab in patients with advanced unresectable hepatocellular carcinoma.

Methods Patients with confirmed HCC in Barcelona Clinic Liver Cancer stage C were included. Patients were initially treated with TACE, followed by intravenous tislelizumab (200 mg, IV) every 21 days and lenvatinib (8 or 12 mg/day) once daily. The primary endpoint was objective response rate based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The secondary endpoints included disease control rate based on mRECIST, objective response rate and disease control rate based on the Response Evaluation Criteria in Solid Tumors (version 1.1), overall survival (OS), progression-free survival (PFS), time to progression (TTP), duration of response (DOR), and safety. An exploratory endpoint was systemic immune-inflammation index (SII).

Results Thirty-one patients with advanced unresectable HCC were enrolled. The objective response rate was 74.2% and disease control rate was 87.1% based on mRECIST. The median OS was 12.6 months and median PFS was 6.5 months. The median TTP was 8.2 months, and median DOR was 7.3 months. Treatment-related adverse events occurred in 64.5% of patients, and most events were grade1-2. The rate of grade ≥3 events was 19.4%. Overall survival and progression-free survival after triple therapy were better in patients with lower SII at baseline.

Conclusion The combination of TACE, lenvatinib, and tislelizumab can be effective against advanced unresectable HCC, leading to a relatively high objective response rate and tolerable safety profile. SII may be useful for predicting response to this triple therapy.

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Keywords Efficacy, Hepatocellular carcinoma, Lenvatinib, TACE, Tislelizumab

Introduction

Hepatocellular carcinoma (HCC), which accounts for 75%–90% of all primary liver cancers [1, 2], typically does not lead to easily recognizable symptoms in the early stages. Consequently 39%–53.6% of patients are diagnosed when the disease has already reached a stage so advanced, most often stage C in the Barcelona Clinic Liver Cancer (BCLC) scheme, that it is considered unresectable and median survival time is only 3.0 to 5.7 months [3–6]. Treatment options for such patients are limited to local or systemic therapies, which often fail to substantially improve prognosis. None of these approaches can reduce the high recurrence rate attributable to the aggressive biological behavior of advanced tumors, nor can they achieve a curative outcome. Therefore, further treatment strategies are required.

New therapeutic options for advanced unresectable HCC (uHCC) have emerged in the form of immune checkpoint inhibitors (ICIs), targeted kinase inhibitors (TKIs) and targeted anti-angiogenic drugs. These approaches may be less effective when applied individually: for example, the objective response rate is only 9.2%–18.8% for ICIs or targeted anti-angiogenic drugs as monotherapies [7–12]. Better efficacy may be achieved by combining ICIs with targeted anti-angiogenic drugs or combining two ICIs [13–15]. The combination of ICIs with TKIs may be more effective than the corresponding monotherapies or placebo, based on the trials LEAP-002 [16], CARES-310 [17], and BGB-A317-211 [18]. Another promising combination against advanced unresectable HCC may be the combination of immunotherapy with transcatheter arterial chemoembolization (TACE). This approach has been reported to lead to objective response rates between 3.9% and 38.9%, median progression-free survival lasting 3.6 to 6.3 months, and median overall survival lasting 5.0 to 15.5 months, with overall survival rates of 36.0%–68.0% at 1 year, 13.0%–22.0% at 3 years, and 5.0%–8.0% at 5 years [19–28].

Recently, the triple therapy combining TACE with TKIs and ICIs has achieved significant breakthroughs in treating advanced uHCC patients. In the phase III EMERALD-1 trial, the combination of durvalumab, bevacizumab and TACE achieved median progression-free survival lasting 15.0 months, with median overall survival not yet reached [29]. Similarly, in the phase III LEAP-012 trial, the combination of lenvatinib, pembrolizumab and TACE was associated with median progression-free survival lasting 14.6 months and with an overall survival rate of 75% at 2 years [30]. Triple therapy holds promise as a new standard treatment for advanced uHCC patients. However, clinical evidence for this approach in advanced uHCC remains limited. Therefore, this study enrolled patients with advanced uHCC to utilize conversion therapy with TACE combined with ICIs and TKIs. This aims to, on one hand, convert advanced uHCC into a manageable chronic disease state enabling long-term survival, and on the other hand, create the potential for subsequent surgical intervention.

Given these promising reports about the efficacy of triple therapy against advanced unresectable HCC, we assessed the efficacy of the combination of TACE, ICIs and TKIs in patients at our medical center. We focused on the ICIs tislelizumab, which is an antibody against the programmed death 1 (PD-1) receptor that can reduce antibody-dependent phagocytosis [31] and which was clinically licensed in China as first-line treatment against unresectable or metastatic HCC based on the global phase III RATIONALE-301 trial. In this trial, tislelizumab alone was associated with overall survival that was non-inferior to that with sorafenib alone [8], and it achieved longer median duration of response (36.1 months) than ICI-based combination therapies in phase III trials (10–22 months) [9–11]. We gave our patients both tislelizumab and lenvatinib, because this combination was associated with an objective response rate of 38.7% and overall survival rate of 88.6% at 12 months in the BGB-A317-211 study [18]. To this dual therapy we added TACE in order to improve efficacy further.

Methods

Study design

This was a single-center, single-arm, open-label, prospective, exploratory clinical trial conducted from March 1, 2021, to July 31, 2023 at Guangxi Medical University Cancer Hospital, China. This study was approved by the Medical Ethics Committee at the hospital [approval CS2021 (94)] and conducted in accordance with the principles of the Declaration of Helsinki. The study was registered with ClinicalTrials.gov (NCT05131698). Written informed consent was obtained from all patients before the start of the study.

Eligibility criteria

Patients were included in the study if they (1) were >18 and ≤70 years old, (2) had HCC confirmed through biopsy or clinical diagnosis that was assigned to BCLC stage C, (3) had never received systemic treatment for HCC, (4) had an Eastern Cooperative Oncology Group performance score (ECOG PS) ≤ 1, (5) were expected to live longer than 3 months, (6) had at least one lesion that could be assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), (7) had

Child-Pugh A or B liver function within 7 days before receiving the first study treatment, (8) were judged eligible for TACE, and (9) were able and willing to provide written informed consent.

Patients were excluded from the study if they presented any of the following: (1) other malignancies concurrent with HCC or during the previous 5 years, (2) participation in other drug trials during the previous 4 weeks, (3) history of bleeding or a bleeding event of grade 3 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) within the previous 4 weeks, (4) contraindications to TACE, or (5) hypersensitivity to human or murine monoclonal antibodies.

Treatment regimens

All patients were first treated with TACE, and the day of treatment was defined as day 1. During TACE, the femoral artery was punctured and the following drugs were delivered: lobaplatin (30 mg/m^2), raltitrexed (4 mg), and lipiodol (5 mL). At the discretion of the clinician, TACE was repeated at intervals longer than 6 weeks for no more than six treatments altogether.

All patients received lenvatinib (Eisai) starting on day 4 at an initial dose of 12 mg once daily if body weight was ≥60 kg or 8 mg once daily otherwise. All patients also received tislelizumab (BGB-A317; BeOne Medicines) starting on day 5 as intravenous infusion (200 mg) once every 3 weeks.

Study treatment was discontinued if any of the following events occurred: pregnancy, withdrawal of informed consent, disease progression based on imaging, or intolerable toxicity following dose adjustment.

Study endpoints

The primary endpoint was objective response rate (ORR) according to mRECIST criteria, including cases of complete response (CR) and partial response (PR). Secondary endpoints were disease control rates (DCR) according to mRECIST and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, ORR according to version 1.1 of RECIST criteria, overall survival (OS), progression-free survival (PFS), time to progression (TTP), duration of response (DOR), and safety.

DCR was defined as the percentage of patients, among those who could be evaluated for response, who achieved CR, PR, or stable disease (no progression for longer than 4 weeks). Patients who could be evaluated for response were defined as those who received at least 5 cycles of tislelizumab (15 weeks) and whose tumors were assessed after 2 cycles of tislelizumab (6 weeks). Patients who achieved complete or partial response or stable disease had to be re-examined 3 weeks later.

OS was defined as the time from day 1 until any-cause death or the last known date alive. Progression-free survival was defined as the time from day 1 until first documented progression or any-cause death. Time to progression was defined as the time from day 1 until first documented progression, not including death. DOR was defined as the interval between first documented complete or partial response and first documented progression or any-cause death.

An exploratory endpoint in this study was the systemic immune-inflammation index (SII), which has been proposed as a way to predict response to combination therapy [32]. It reflects the relationship between inflammatory and immune responses in the body and is calculated from routine peripheral blood analysis as:

$$\mathrm{SII} = (\text{neutrophil count} \times \text{platelet count}) / \text{lymphocyte count}$$

Patients were dichotomized into those showing SII lower or higher than the optimal value from receiver operating characteristic curves and the Youden index (see below), then overall survival and progression-free survival were compared between the two groups.

Treatment efficacy and time until discontinuation were evaluated every 6 weeks. Computed tomography and other imaging examinations were performed at the end of every 2 cycles. Data were also collected on other laboratory tests, vital signs, electrocardiography, and adverse events. Adverse events were evaluated according to the CTCAE (version 5.0).

Rate of conversion, referring to how many patients became eligible for hepatic resection as a result of the triple therapy, was not an endpoint of this study because our focus was on the efficacy and safety of the triple therapy itself.

Follow-up

Patients were followed up every 3 months during the first 12 months after the end of the triple therapy, and every 6 months thereafter. The last follow-up was 3 years after enrollment of the last patient. The following parameters were recorded during the follow-up period: survival, time to disease progression or death, and serious adverse events.

Statistical analysis

The minimal sample for this study was estimated as follows. Given an objective response rate below 20% for lenvatinib monotherapy as first-line treatment for advanced HCC [7], we hypothesized that its combination with tislelizumab and TACE would Lead to an objective response rate above 40%. The binomial test indicated a minimal sample of 28 patients to detect an increase from

20 to 40% with at least 80% power and one-sided type I error of 0.05. This number was increased to 31 to account for a 10% dropout rate.

Data in the study were analyzed statistically through 2-sided testing in SPSS or R software. The time-to-event variables of overall and progression-free survival as well as duration of response were analyzed using the Kaplan–Meier method. Safety outcomes were reported as numbers and percentages. Rates of objective response and disease control, together with their corresponding 95% confidence interval (CI), were calculated using the Clopper–Pearson method. Differences were considered significant if associated with $p < 0.05$.

The optimal value of SII for dichotomizing patients was determined from receiver operating characteristic curves and the Youden index.

Results

A total of 31 patients with HCC in BCLC stage C were enrolled and treated with the combination of TACE, lenvatinib, and tislelizumab (Fig. 1). The median follow-up time was 18.3 months. Among the 31 patients, 22 (71.0%) had maximum tumor diameter of ≥10 cm, and 19 (61.3%) had multiple tumor lesions. The majority of patients (80.6%) suffered from vascular invasion, and 17 (54.8%) had a portal vein tumoral thrombus. Extrahepatic metastasis occurred in 14 patients (45.2%). In addition, 28 patients (90.3%) were positive for hepatitis B virus (HBV), and 27 (87.1%) had hepatic cirrhosis. The baseline characteristics of all 31 patients are presented in Table 1.

Efficacy

Tumor response was assessed according to the criteria of mRECIST and RECIST version 1.1 (Table 2). Based on mRECIST, the ORR was 74.2% and DCR was 87.1%. Two patients achieved CR; 21 patients achieved PR; and 4 patients achieved stable disease (SD). The remaining 4 experienced progressive disease (PD). The best percentage change in target lesion size relative to baseline is shown in Fig. 2A. Median OS was 12.6 months (95% CI, 9.17 - not reached), while OS rates were 87.1% at 6 months, 53.0% at 1 year, and 26.5% at 2 years (Fig. 3A). Median PFS was 6.5 months (95% CI, 4.93 – 11.5), while PFS rates were 54.8% at 6 months, 27.7% at 1 year, and 27.7% at 2 years (Fig. 3B). Median TTP was 8.2 months, and median DOR was 7.3 months.

Based on RECIST version 1.1, the ORR was 67.7% and DCR was 87.1%. One patient achieved CR; 20 patients achieved PR; and 6 patients achieved SD. The remaining 4 experienced PD. The best percentage change in target lesion size relative to baseline is shown in Fig. 2B.

Safety

Among all enrolled patients, 20 (64.5%) experienced treatment-related adverse events (TRAEs), most of which

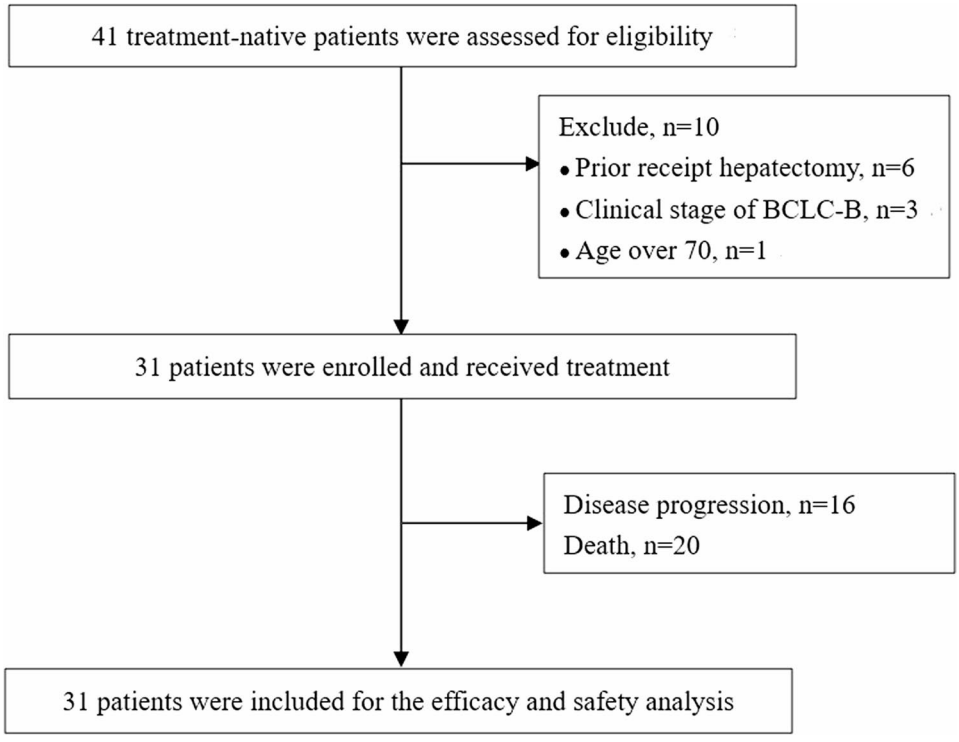

Fig. 1 Flow chart of study design

Table 1 Baseline characteristics of the patients

Characteristics	All patients ($n=31$)
Sex	
Female	1 (3.2%)
Male	30 (96.8%)
Age, years	
<50	16 (51.6%)
≥50	15 (48.4%)
HBV	
Negative	3 (9.7%)
Positive	28 (90.3%)
HCV	
Negative	31 (100.0%)
Positive	0 (0.0%)
Largest tumor diameter, cm	
<10	9(29.0%)
≥10	22(71.0%)
Number of tumors	
Multiple	19 (61.3%)
Single	12 (38.7%)
Hepatic cirrhosis	
Negative	4 (12.9%)
Positive	27 (87.1%)
AFP, ng/mL	
≤400	9 (29.0%)
>400	22 (71.0%)
Vascular invasion	
Negative	6 (19.4%)
Positive	25 (80.6%)
Portal vein tumoral thrombus	
Negative	14 (45.2%)
Positive	17 (54.8%)
Child-Pugh grade	
A5	13 (41.9%)
A6	11 (35.5%)
B7	4 (12.9%)
B8	3 (9.7%)
Extrahepatic metastasis	
Negative	17 (54.8%)
Positive	14 (45.2%)
Lung metastasis	
Negative	23 (74.2%)
Positive	8 (25.8%)
Lymphatic metastasis	
Negative	23 (74.2%)
Positive	8 (25.8%)
Total bilirubin, μmol/L	
≤17.1	13 (41.9%)
>17.1	18 (58.1%)
Alanine transaminase, U/L	
≤40	13 (41.9%)
>40	18 (58.1%)
Aspartate transaminase, U/L	
≤40	4 (12.9%)
>40	27 (87.1%)

Table 1 (continued)

Characteristics	All patients (*n* = 31)
Albumin, g/L	
<35	16 (51.6%)
≥35	15 (48.4%)
Prothrombin time, seconds	
≤13.1	15 (48.4%)
>13.1	16 (51.6%)
SII*	
>608.7	15 (48.4%)
≤608.7	16 (51.6%)

AFP alpha fetoprotein, *BCLC* Barcelona Clinic Liver Cancer, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *SII* systemic immune-inflammation index

* Optimal value was determined to be 608.7 based on receiver operating characteristic curves and the Youden index

Table 2 Effectiveness of tumors in patients after treatment

Variables	All patients (*n* = 31)	
	mRECIST	RECIST 1.1
Confirmed objective response, *n* (% [95% CI])	23 (74.2 [57.9,90.5])	21 (67.7 [50.3,85.2])
Complete response, *n* (%)	2 (6.5)	1 (3.2)
Partial response, *n* (%)	21 (67.7)	20 (64.5)
Stable disease, *n* (%)	4 (12.9)	6 (19.4)
Disease control, *n* (% [95% CI])	27 (87.1 [74.6,99.6])	27 (87.1 [74.6,99.6])
Progressive disease, *n* (%)	4 (12.9)	4 (12.9)

mRECIST modified Response Evaluation Criteria in Solid Tumors, *RECIST* Response Evaluation Criteria in Solid Tumors, *CI* confidence interval, *NA* not applicable, *PFS* progression free survival, *OS* overall survival

were grade 1–2 in severity (Table 3). The most frequent TRAEs were elevated levels of γ-glutamyl transpeptidase (11 patients, 35.5%) or aspartate aminotransferase (10, 32.3%) as well as thrombocytopenia (8, 25.8%). Six patients (19.4%) experienced grade 3 TRAEs, the most frequent being hand-foot syndrome (9.7%), pneumonia (6.5%), and hypertension (3.2%). Serious TRAEs were reported in 2 patients, both of whom were pneumonia patients with grade 3 TRAEs, necessitating discontinuation of lenvatinib and tislelizumab.

Relationship between SII and the efficacy of triple therapy

We explored whether the recently described SII might be useful for predicting the efficacy of triple therapy. Patients were dichotomized into those with SII values below or above the optimal value of 608.7, which was determined from receiver operating characteristic curves and the Youden Index. This optimal value gave an area under the curve of 0.605, sensitivity of 0.600 and specificity of 0.273. The median PFS was significantly longer among those with lower SII values than among those with higher values (10.7 vs. 4.9 months, $P = 0.026$; Supplementary Fig. S1). A similar tendency was observed for median OS, although it did not achieve statistical significance (14.7 vs. 12.6 months, $P = 0.082$; Supplementary Fig. S2).

Discussion

The results of this phase II study demonstrate that the triple combination of TACE followed by lenvatinib and tislelizumab may be clinically effective against HCC in BCLC stage C, providing an objective response rate of 74.2% as per mRECIST. This rate is substantially higher than the 29%–46% reported for other first-line combination therapies in previously published studies and ongoing phase II clinical trials [33–36]. Median overall survival in our study lasted 12.6 months, which is shorter than the 19.2 months in the IMbrave150 study [10], 21.2 months in the LEAP-002 study [16] and 22.1 months in the CARES-310 study [17]. Median progression-free survival in our cohort lasted 6.5 months, comparable to the 8.2 months in the LEAP-002 trial [16] and 5.8 months in the CARES-310 study [17], but considerably shorter than the 14.6 months in the LEAP-012 study [30] and 15.0 months in the EMERALD-1 trial [29]. The shorter survival in our cohort compared to some other trials may reflect the fact that all our patients were in BCLC stage C and most presented risk factors for poor prognosis in advanced unresectable HCC: 71.0% of the 31 patients had a maximum tumor diameter ≥ 10 cm, 61.3% had multiple tumor lesions, and more than half had portal vein cancer thrombus, all of which were high-risk factors indicating poor prognosis of advanced uHCC.

Despite these poor baseline characteristics, the triple therapy achieved satisfactory efficacy, which could be attributed to at least three reasons. One is that extent of tumor vascularization may be particularly effective at predicting efficacy. The tumors in our patients showed abundant blood supply, even if most tumors showed vascular invasion and portal vein cancer thrombi. TACE can better embolize well vascularized tumors, and the lipiodol can induce necrosis in a larger number of tumor cells, leading to greater release of tumor antigens and

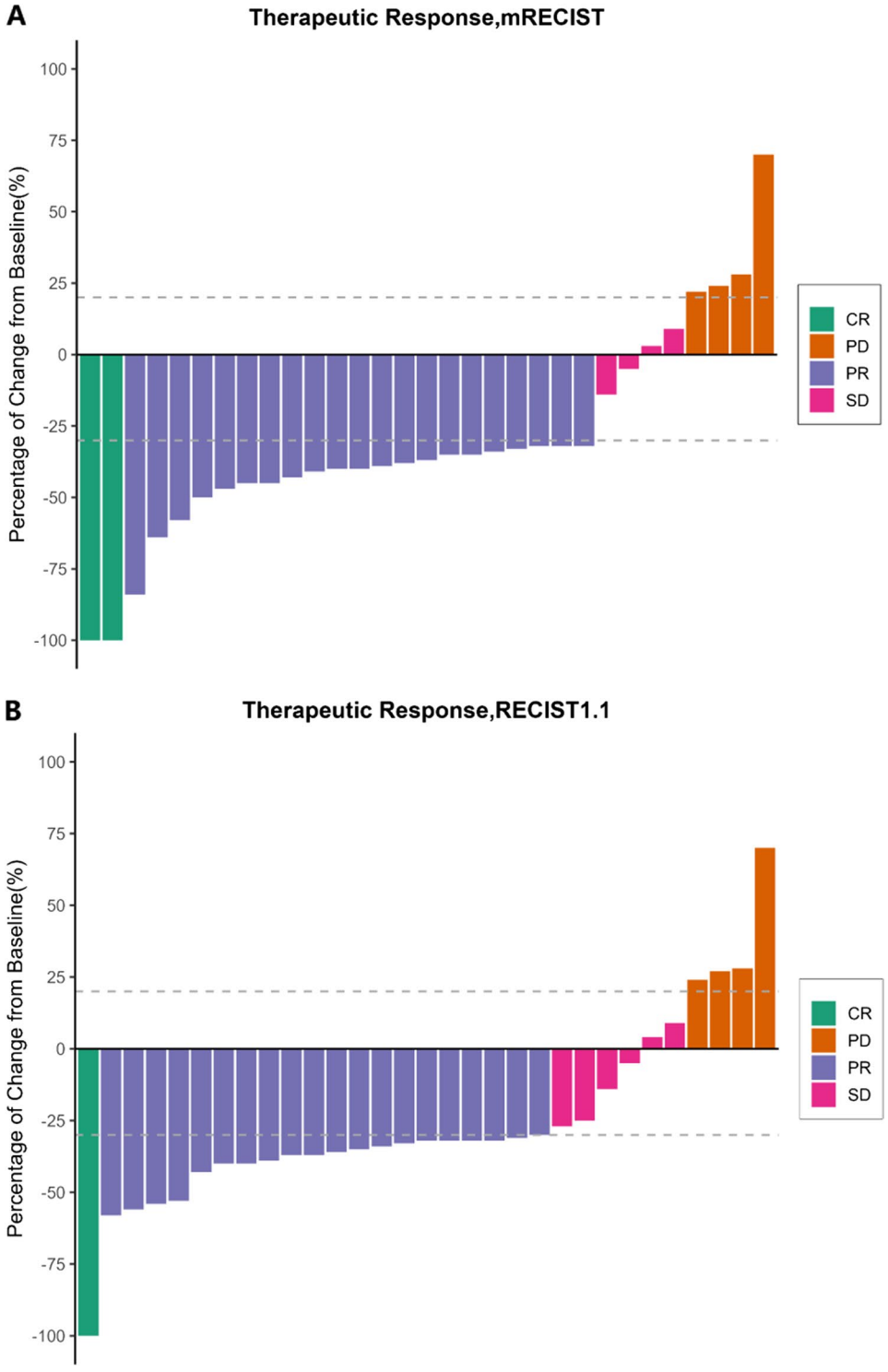

Fig. 2 The best percentage change in target lesion size relative to baseline assessed according to (**A**) mRECIST criteria and (**B**) RECIST1.1 criteria CR, complete response, PD, progressive disease, PR, partial response, SD, stable disease

thus induction of more anti-tumor T cells. A second reason for the efficacy of triple therapy may be the fact that an ECOG PS score of 0 and Child-Pugh class A liver function are associated with higher efficacy. This could be due to better immune function, stronger mobilization of the immune system after activation, and higher tolerance of various treatments. In such patients, triple therapy can induce a large number of T cells expressing

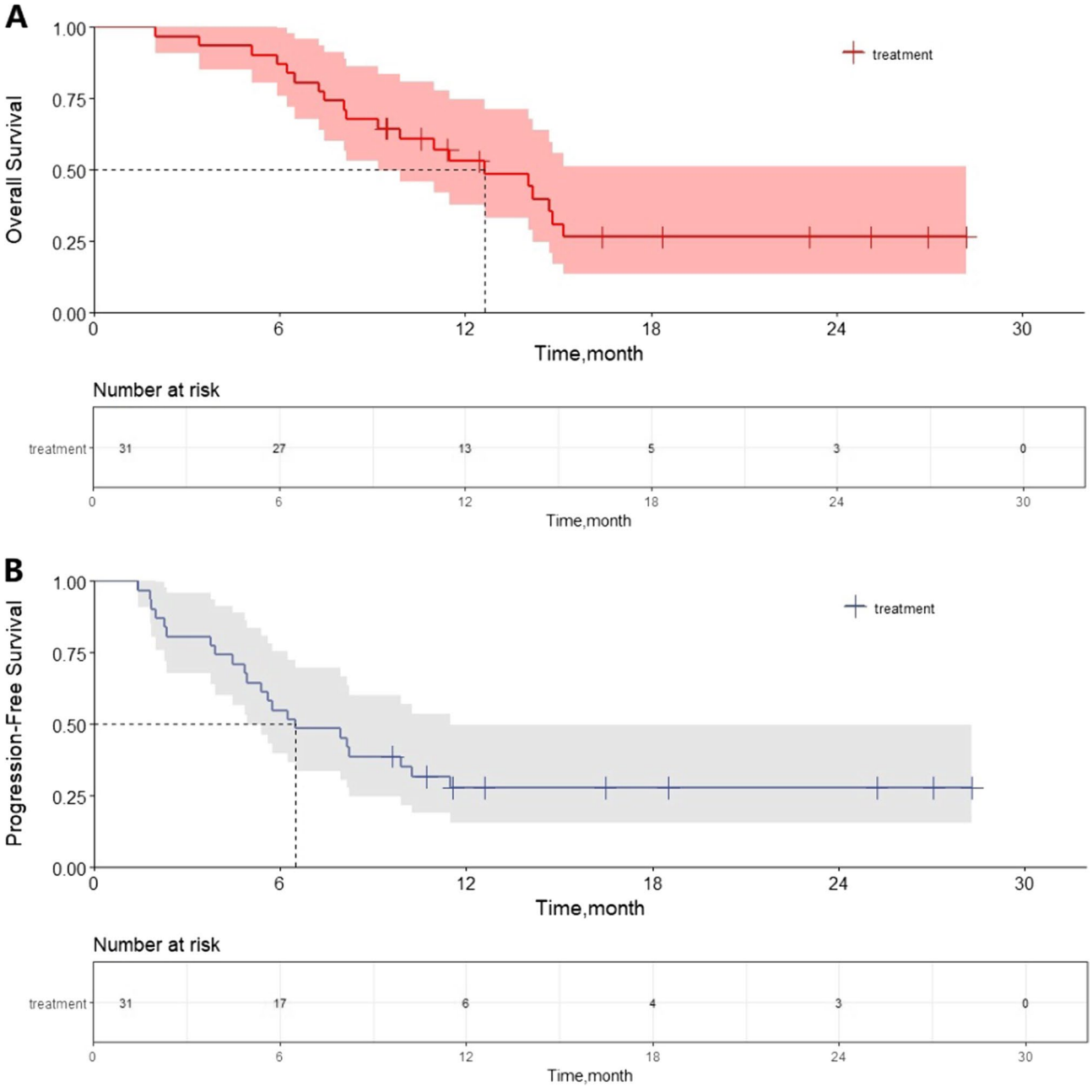

Fig. 3 Kaplan–Meier analysis for OS (**A**) and PFS (**B**) was performed according to the investigator assessments for the full analysis set.OS, overall survival; PFS, progression free survival

abundant PD-1 on the surface to reach the lesion site, so the use of PD-1 inhibitors can improve therapeutic efficacy. Evidence from clinical studies indicates that PD-1 inhibitor and TKI therapy demonstrates favorable efficacy in HCC patients with Child-Pugh class A and B [37–41]. In fact, our results suggest that the triple therapy can be safe and effective even in patients with Child-Pugh B liver function. For patients with Child-Pugh B liver function, the core clinical challenge lies in balancing efficacy and safety, as hepatic impairment may increase the risk of treatment-related hepatotoxicity and could even precipitate liver failure. The inclusion of this population in our study allows for a targeted evaluation of the tolerability of the triple combination of TACE, lenvatinib, and tislelizumab regimen in patients with moderate hepatic impairment, as well as the necessity for dose adjustments. Simultaneously, by analyzing efficacy data in this population, we can determine whether the regimen provides clinical benefit for patients with poorer liver function, thereby informing the optimization of subsequent treatment strategies. A third reason for the efficacy of triple therapy may be that we applied first the interventional

Table 3 Summary of treatment-related adverse events

Treatment-related adverse events, *n* (%)	All patients (*n* = 31)				
	Any grade	Grades 1 and 2	Grade 3	Grade 4	Grade 5
Increased γ-glutamyl transpeptidase	11 (35.5)	11 (35.5)	0 (0)	0 (0)	0 (0)
Increased aspartate aminotransferase	10 (32.3)	10 (32.3)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	8 (25.8)	8 (25.8)	0 (0)	0 (0)	0 (0)
Increased alanine aminotransferase	7 (22.6)	7 (22.6)	0 (0)	0 (0)	0 (0)
Anemia	7 (22.6)	7 (22.6)	0 (0)	0 (0)	0 (0)
Increased total bilirubin	6 (19.4)	6 (19.4)	0 (0)	0 (0)	0 (0)
Leukopenia	6 (19.4)	6 (19.4)	0 (0)	0 (0)	0 (0)
Decreased appetite	6 (19.4)	6 (19.4)	0 (0)	0 (0)	0 (0)
Vomiting	5 (16.1)	5 (16.1)	0 (0)	0 (0)	0 (0)
Diarrhea	4 (12.9)	4 (12.9)	0 (0)	0 (0)	0 (0)
Nausea	3 (9.7)	3 (9.7)	0 (0)	0 (0)	0 (0)
Hand-foot syndrome	3 (9.7)	0 (0)	3 (9.7)	0 (0)	0 (0)
Hyperglycemia	3 (9.7)	3 (9.7)	0 (0)	0 (0)	0 (0)
Hypertension	3 (9.7)	2 (6.5)	1 (3.2)	0 (0)	0 (0)
Pyrexia	2 (6.5)	2 (6.5)	0 (0)	0 (0)	0 (0)
Fatigue	2 (6.5)	2 (6.5)	0 (0)	0 (0)	0 (0)
Pneumonia	2 (6.5)	0 (0)	2 (6.5)	0 (0)	0 (0)
Rash	1 (3.2)	1 (3.2)	0 (0)	0 (0)	0 (0)
Pruritus	1 (3.2)	1 (3.2)	0 (0)	0 (0)	0 (0)

therapy, followed as soon as possible by the targeted therapy and immunotherapy. This approach may help the three treatments synergize: the interventional therapy may release large amounts of tumor antigen, against which the targeted and immune therapies can act.

Most patients in our study experienced TRAEs of grade 1/2 severity and only 19.4% experienced TRAEs of grade 3, which indicates less frequent TRAEs than in the IMbrave150 and other trials. These results suggest that the triple therapy in our study is well tolerated and may be less toxic than other first-line treatments for unresectable HCC. In fact, most of the patients who experienced grade 3 TRAEs achieved PR, which may explain why patients with advanced HCC after severe TRAEs can have a better antitumor effect. In general, TRAEs after ICI therapy have been associated with better prognosis [42, 43], inducing higher rates of objective response and disease control [42, 44], which may reflect that T cells are more active in patients experiencing more severe TRAEs, leading to stronger antitumor efficacy [45].

Our study associated lower SII with significantly longer progression-free survival and a tendency toward longer overall survival after triple therapy. In other words, patients with lower SII levels may benefit more from triple therapy than those with higher levels. SII has been proposed as an indicator of systemic inflammation [46], and the systemic inflammatory response has been linked to survival of cancer patients after tumor resection [47–49]. Our findings are consistent with previous studies suggesting that SII can predict tumor progression and treatment response [50–52], but they should be validated and extended in larger samples in order to establish the clinical utility and prognostic relevance of SII.

Our study aimed to examine the efficacy and safety of our triple therapy on its own, but it also provides anecdotal evidence that the triple therapy may be useful for converting initially unresectable HCC into resectable disease. One patient in our cohort achieved complete response per mRECIST after 2 cycles of immunotherapy, after which maintenance therapy was continued for 10 cycles. The intrahepatic lesion remained stable, and overall survival reached 26.9 months by last follow-up, demonstrating that maintenance immunotherapy can enable long-term survival. Another patient achieved partial response per mRECIST after 3 immunotherapy cycles. The patient then underwent second TACE without tumor regression, followed by radical resection, which led to tumor-free status. Overall survival reached 9.4 months by last follow-up, suggesting that surgery can be a viable strategy during treatment plateau. Some other patients in our cohort might have been eligible for surgery, but the attending physicians considered it unwise given the presence of vascular invasion, vascular tumor thrombi, extrahepatic metastasis or other conditions; or the patients themselves were unwilling to consider it because of the risks involved or financial constraints. Therefore, conversion rate was not systematically analyzed in this study. Nevertheless, our anecdotal examples highlight the need to explore in which patients our triple therapy can be an effective conversion therapy and what are the optimal subsequent treatments to maximize survival.

Our findings suggest that predicting efficacy of triple therapy means much more than differentiating between intermediate or advanced HCC. In our cohort, better efficacy was associated with better liver function; with relatively concentrated tumor lesions, such as lesions confined to half of the liver or a certain liver segment, which may reflect better embolization; and with the absence of distant metastases, especially lung metastases. These findings may help personalize treatment of patients with HCC in BCLC stage C. Secondly, whether patients achieving CR require maintenance therapy and the optimal duration of such therapy remain uncertain, necessitating long-term observation. Furthermore, for patients achieving PR with combination therapy who have an opportunity for surgery, how to determine the optimal surgical window of opportunity to enable long-term survival requires further exploration. Finally, how to adjust the treatment regimen for patients who experience progression after therapy is another important consideration. Whether adding radiotherapy to triple therapy can improve tumor control efficacy also needs further investigation. Hepatic Arterial Infusion Chemotherapy (HAIC) has also demonstrated a promising DCR in the treatment of advanced HCC [53]. Whether HAIC can achieve satisfactory results when integrated into triple therapy combining targeted and immunotherapeutic agents will be a focus of our further research.

This study has some limitations that warrant mention. Firstly, the sample size is relatively small, and more samples are needed to further validate the study findings. Moreover, as this is a single-arm study lacking a control arm, there is a potential for some degree of bias. Therefore, large-scale, multicenter, prospective, randomized studies are required to validate the findings of this research. Secondly, this study acknowledges that the SII cutoff value derived from the ROC curve and Youden index has certain limitations in clinical application. The area under the curve (AUC) was at a relatively low level, indicating that this cutoff value has weak discriminatory power for disease outcomes, making it difficult to accurately identify patients who may benefit or be at risk. Another factor is its suboptimal specificity, meaning that in practical applications, this threshold may misclassify a significant number of non-target individuals as target patients. This could lead to a high false-positive rate in clinical decision-making, potentially increasing the risk of unnecessary interventions or overtreatment. Nevertheless, based on our analysis of enrolled cases, SII likely has a significant association with disease outcomes. Therefore, we included this indicator as one of our exploratory objectives. This SII cutoff value urgently requires validation in larger independent cohorts. Notably, this study did not explore immunotherapy-specific biomarkers. Given the established critical role of Programmed Death-Ligand 1 (PD-L1) expression levels in predicting immunotherapeutic efficacy, comprehensive evaluation of PD-L1 as a predictive biomarker remains essential in subsequent translational studies. Finally, this study utilized the ECOG score and Child-Pugh grade as core assessment indicators for patients' physical fitness and liver function. Although both demonstrate high efficiency and generalizability in clinical practice, they exhibit limited sensitivity to systemic body composition changes. In recent years, the prognostic value of abnormal body composition in HCC management has gained significant attention: Sarcopenia may compromise clinical outcomes by reducing treatment tolerance and increasing adverse event risks [54], while myosteatosis correlates closely with inflammatory states and metabolic dysregulation, potentially diminishing therapeutic response to immune checkpoint inhibitors or targeted agents [55, 56]. Multiple studies confirm that incorporating body composition analysis into baseline assessments significantly enhances prediction accuracy for treatment outcomes (e.g., OS, ORR) [56, 57]. The failure to incorporate these metrics in the current study constitutes a limitation, potentially leading to incomplete characterization of patients' functional status.

Despite the limitations of the present study, it provides strong evidence that the triple combination of TACE, lenvatinib, and tislelizumab can be safe and effective against HCC in BCLC stage C. Our results suggest the possibility that SII can be used to predict efficacy of triple therapy and that triple therapy may be worth exploring as a conversion therapy, both of which should be examined in larger studies.

Supplementary Information

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Supplementary Material 1. Supplementary Fig. S1. The PFS curves of SII-low group and SII-high groupPFS, progression free survival; SII, systemic inflammation index. Supplementary Fig. S2. The OS curves of SII-low group and SII-high groupOS, overall survival; SII, systemic inflammation index.

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Authors' contributions

(I) Conception and design: Zhiming Zhang, Yumei Zhang; (II) Administrative support: Zhiming Zhang; (III) Provision of study materials or patients: Xiang Nong, Yu Yao; (IV) Collection and assembly of data: Jinlong Xie, Jingchang Liang; (V) Data analysis and interpretation: Jingchang Liang, Yu Yao, Xiang Nong; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors. All authors reviewed the manuscript.

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Data availability
Original data are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of Guangxi Medical University Cancer Hospital (ethics number: CS2021 (94)) and conducted in accordance with the principles of the Declaration of Helsinki. The study was registered with ClinicalTrials.gov (NCT05131698).

Competing interests
The authors declare no competing interests.

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