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RESEARCH

Transarterial chemoembolization combined with sintilimab and lenvatinib for the treatment of unresectable hepatocellular carcinoma: a retrospective study

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Abstract

Background The treatment of unresectable hepatocellular carcinoma (uHCC) challenging due to unfulfilled clinical requirements.

Objective To evaluate the safety and efficacy of combining transarterial chemoembolization (TACE) with sintilimab and lenvatinib in the treatment of uHCC.

Methods We retrospectively analyzed the data of patients with uHCC who were treated with a combination of TACE, sintilimab, and lenvatinib between May 2019 and December 2021 at the Chinese PLA General Hospital. Systemic treatment was started 1 week after TACE was performed. Sintilimab was administered intravenously at a dosage of 200 mg every three weeks, and lenvatinib was given orally at dosages of 8 mg or 12 mg daily, contingent upon the weight of the patients. The primary endpoint was the objective response rate (ORR) as per the mRECIST. Secondary endpoints were disease control rate (DCR), progression-free survival (PFS), overall survival (OS) and treatment-related adverse events (tr-AEs).

Results A total of 32 patients were enrolled in the study. Among them, 9 patients were classified as Barcelona Clinic Liver Cancer-B (BCLC-B), 23 patients were classified as BCLC-C, 14 patients diagnosed with portal vein tumors, and 12 patients were diagnosed with extra hepatic metastases. The ORR and DCR were 75% and 90.6% respectively, with 4 patients exhibiting (12.5%) complete response, 20 patients exhibiting (62.5%) partial response, 5 patients exhibiting (15.6%) stable disease, and 3 patients exhibiting (9.4%) progressive disease. With a median follow-up time of 19.6 months, the median PFS was 9.9 months, and the median OS was 33.3 months. A total of 31 patients experienced different degrees of tr-AEs, of which 2 were grade 3 tr-AEs.

Conclusion The combination therapy of TACE, sintilimab, and lenvatinib demonstrates satisfactory efficacy in the treatment of uHCC with manageable tr-AEs.

Keywords Unresectable hepatocellular carcinoma · TACE · Sintilimab · Lenvatinib · Combination therapy

Abbreviations

AE	Adverse event
BCLC	Barcelona Clinic Liver Cancer

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CR	Complete response
CT	Computed tomography
DCR	Disease control rate
ECOG PS	Eastern Cooperative Oncology Group Performance Status
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICI	Immune Checkpoint Inhibitor
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
NCI-CTCAE V5.0	National Cancer Institute's Common Terminology Criteria for Adverse Events. Version 5.0
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-ligand 1
PFS	Progression-free survival
PR	Partial response
SD	Stable disease
TACE	Transarterial chemoembolization
TKI	Tyrosine Kinase Inhibitor
tr-AEs	Treatment-related adverse events
uHCC	Unresectable hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) constitutes approximately 90% of primary liver malignancies and is the fourth leading cause of malignancy-related mortality worldwide, and the second leading cause among men (Bray et al. 2018). The insidious onset of HCC results in about 70% of patients being diagnosed in the middle to advanced stages, depriving them of the opportunity for surgical resection (Colecchia et al. 2014).

Transarterial chemoembolization (TACE) is a widely utilized non-surgical treatment for liver cancer. It works by obstructing the blood supply to HCC, thereby inducing tumor cell necrosis through the deprivation of essential nutrients and oxygen. However, the hypoxic tumor microenvironment formed after TACE can also stimulate angiogenesis (Maxwell et al. 1997), and potentially attract immunosuppressive cells (Kwilas et al. 2015). This may significantly contribute to the high recurrence rate of HCC after TACE treatment. In recent years, the combination therapy of TACE with systemic anti-tumor therapy has gained prominence as an approach to enhance treatment efficacy. Lenvatinib is a multikinase inhibitor targeting tumor angiogenesis. It has demonstrated remarkable efficacy for un-resectable HCC (uHCC) in a global open-label randomized phase III study (REFLECT) (Kudo et al. 2018). There is existing evidence suggesting that the combination therapy of TACE with lenvatinib for uHCC yields superior clinical outcomes in comparison to TACE or lenvatinib monotherapy (Fu et al. 2021; Peng et al. 2023). Furthermore, Programmed Death-1 (PD-1) and Programmed Death-ligand 1 (PD-L1) inhibitors such as sintilimab, camrelizumab, tislelizumab, toripalimab, nivolumab, and pembrolizumab can block the PD-1/PD-L1 signaling pathway, leading to the restoration of the immune system's anti-tumor activity (Li et al. 2022). The efficacy of PD-1/PD-L1 inhibitors in treating advanced HCC has been clinically validated (Commission and of NH 2022). The impact of TACE on the tumor immune microenvironment, such as the up-regulation of PD-L1 expression on tumor cells, is widely recognized (Kwilas et al. 2015). Therefore, combining PD-1/PD-L1 inhibitors with TACE may also have the potential to further synergistically enhance the therapeutic efficacy. Thus, there is currently a rising interest in investigating the triple therapy approach of combining TACE with lenvatinib and PD-1/PD-L1 inhibitors to further improve the survival outcomes for patients with uHCC.

In China, combination therapies such as "atezolizumab with bevacizumab," "sintilimab with bevacizumab biosimilar," and "pembrolizumab with lenvatinib" have already been recommended as the first-line treatment for advanced HCC (Commission and of NH 2022). Combination therapy of sintilimab with lenvatinib is also commonly used in clinical practice. In the present retrospective study, the aim is to evaluate the efficacy and safety of TACE in combination with sintilimab and lenvatinib in the treatment of uHCC.

Method

Patients

This retrospective analysis includes a cohort of patients who were diagnosed with uHCC between May 2019 and December 2021. They were treated with TACE in combination with sintilimab and lenvatinib at the Chinese People's Liberation Army General Hospital. Inclusion criteria for the study were as follows: 1. HCC diagnosed according to the practice guidelines published by the American Liver Association in 2018 (Marrero et al. 2018). 2. Age of patients between 18 and 75 years. 3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) $\leq$ 1. 4. Barcelona Clinic Liver Cancer (BCLC) stage B or C. 5. Child–Pugh grade A or B. 6. Presence of at least one measurable target lesion. 7. Patients must have been treated with TACE in combination with sintilimab and lenvatinib. Exclusion criteria of the study were as follows: 1. Severe liver dysfunction. 2. Complete blockage

of the main portal vein. 3. Bleeding tendency or coagulation dysfunction. 4. Verified infiltration of the biliary duct. 5. Absence of complete clinical data. The ethical approval was waived by the Ethics Committee of the Chinese People's Liberation Army General Hospital. Informed consent was not required due to the retrospective nature of the study.

TACE

All patients underwent TACE initially, which was performed by Prof. Zhijun Wang, a highly experienced clinician who has 20 years of clinical experience. The right femoral artery was punctured using a modified Seldinger's technique, and a 4F catheter (RH, Terumo Corporation, Japan) was inserted to carry out superior mesenteric artery and hepatic artery angiography to observe the normal condition of the portal vein and identify the arteries supplying the tumor. A 2.7-F microcatheter (RH, Terumo Corporation, Japan) was inserted and carefully navigated to the sub segmental or segmental branches of the artery supplying the tumor. A combination of two to five chemotherapeutic agents including mitomycin, pirarubicin, oxaliplatin, 5-fluorouracil and calcium folinate were mixed with 3–15 ml of lipiodol (Laboratorie Guerbet, Aulnay-sous-Bois, France) and injected into the tumor-feeding artery through a microcatheter in a 1:1 ratio, adjusted based on the tumor size. This procedure was continued until visualization of small portal branches surrounding the tumor was achieved. Finally, the artery feeding the tumor was embolized using gelatin sponge and/or polyvinyl alcohol particles until complete arterial arrest was observed.

TACE was repeated "on request" after the confirmation of a viable tumor by follow-up contrast-enhanced abdominal CT or MRI in patients without deteriorated performance status or organ function. Some patients suffered poor tumor control after the first TACE treatment. The physician will evaluate whether these patients are suitable for TACE treatment again, and will administer a second TACE treatment to those who are suitable and agree to be treated again.

Systemic treatment

Systemic therapy was initiated seven days following the TACE procedure. Patients received an intravenous infusion of sintilimab at a dosage of 200 mg every three weeks. Concurrently, lenvatinib was administered orally at a dosage of 8 mg daily for patients weighing less than 60 kg, or 12 mg daily for patients weighing 60 kg or more. The dosage was adjusted or discontinued based on the severity of the adverse event (AE). All patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection were administered antiviral therapy.

Follow-up

Patients were initially followed up at 4–6 weeks post treatment and then at intervals of 2–3 months thereafter. The endpoint of the follow-up period was determined either by the death of the patient or the last follow-up date. During follow-up, tumor necrosis was evaluated using enhanced CT or MRI scans. The presence of iodine oil deposition or absence of arterial enhancement within the lesion during the arterial phase of imaging indicated a site of tumor necrosis.

Efficacy and safety assessment

The post-treatment tumor response in patients was assessed using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). Complete response (CR) refers to disappearance of all target lesions with arterial enhancement. Partial response (PR) refers to the reduction of more than 30% of the total diameter of the target lesions with arterial enhancement. Disease progression (PD) refers to increase of more than 20% of the total diameter of the target lesions with arterial enhancement or appearance of new lesions. Stable disease (SD) refers to reduction that does not meet the criteria for PR or increase that does not meet the criteria for PD. Objective response rate (ORR) was defined as the percentage of patients who achieved a tumor response rating for CR and PR. Disease control rate (DCR) was defined as the percentage of patients who achieved a tumor response rating for CR, PR, and SD. Progression-free survival (PFS) was defined as the duration between the start of the treatment and the first occurrence of disease progression or death from any cause. Overall survival (OS) was defined as the duration between the start of treatment and either death from any cause or the end of follow-up. The criteria for evaluating the nature and severity of adverse events were based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.

The primary endpoint was ORR per mRECIST. Secondary endpoints were DCR, PFS, OS and treatment-related adverse events (tr-AEs).

Statistical analysis

All statistical analyses were conducted using IBM SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) and MedCalc 20 (MedCalc Software Ltd). Survival curves for PFS and OS were calculated using the Kaplan–Meier method.

Results

Baseline characteristics

The flow chart of patient enrollment and baseline characteristics of enrolled patients are shown in Fig. 1 and Table 1, respectively. Between February 2020 and December 2021, a total of 53 consecutive patients with uHCC who underwent TACE in combination with administration of sintilimab and lenvatinib were initially screened for eligibility. Of these patients, 21 who met the exclusion criteria were excluded (Fig. 1). Finally, 32 patients were included in the analysis.

Of the 32 patients with evaluable data (mean age, 54.8 years; 29 men and 3 women), 21 patients (65.6%) had ECOG-PS 0 and 11 patients (34.4%) had ECOG-PS 1. Most patients in the study had hepatitis B virus infection (81.2%) and were classified as BCLC stage C (71.9%). Additionally, 19 patients (59.4%) had baseline AFP > 400 ng/ml. The median follow-up time of this study was 19.6 (range, 7.2, 47.1) months.

Efficacy outcomes

Among the 32 patients, as per mRECIST criteria, 4 patients (12.5%) showed CR, 20 patients (62.5%) showed PR, 5 patients (15.6%) showed SD, and 3 patients (9.4%) showed PD, resulting in an ORR of 75.0% and DCR of 90.6% (Table 2). The median PFS was 9.9 months (Fig. 2), and median OS was 33.3 months (Fig. 3). Prior to PFS assessment, the mean number of TACE and systemic treatments were 1.3 times and 4 cycles, respectively. Following evaluation, one patient in the study subsequently underwent surgical resection after receiving the combined treatment. Representative images from patients treated

Table 1 Baseline characteristics

Characteristics	Patients (N = 32)
Mean age (years)	54.8 ± 8.8
Gender, n (%)	
Female	3(9.4)
Male	29(90.6)
ECOG PS, n (%)	
0	21(65.6)
1	11(34.4)
ALBI grade, n (%)	
1	10(31.2)
2	19(59.4)
3	3(9.4)
Pre-treatment AFP (ng/mL), n (%)	
≤ 400	11(34.4)
> 400	19(59.4)
No date	2(6.2)
BCLC, n (%)	
B	9(28.1)
C	23(71.9)
Etiology, n (%)	
Hepatitis B virus	26(81.2)
Hepatitis C virus	1(3.1)
Without	5(15.6)
Maximum tumor size	
< 5	11(34.4)
≥ 5	21(65.6)
Tumor number, n (%)	
1	6(18.8)
2	4 (12.5)
≥ 3	22 (68.7)
Portal vein invasion, n (%)	14 (43.7)
Extrahepatic metastasis, n (%)	12 (37.5)

ECOG PS Eastern Cooperative Oncology Group Performance Status, *ALBI* Albumin-Bilirubin, *AFP* α-Fetoprotein, *BCLC* Barcelona Clinic Liver Cancer

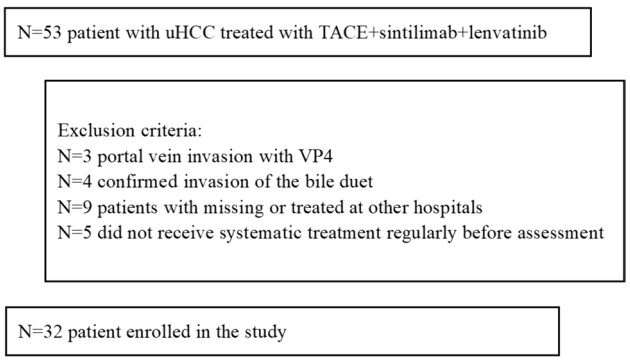

Fig. 1 Flow diagram of patient enrollment

Table 2 Efficacy assessment

Best response, n (%)	Intrahepatic(n = 32)
Complete response	4(12.5)
Partial response	20(62.5)
Stable disease	5(15.6)
Progressive disease	3(9.4)
Objective response rate	24(75.0)

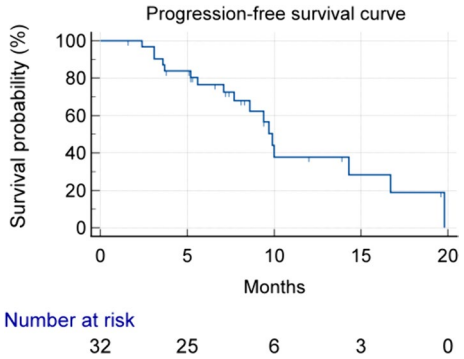

Fig. 2 The Progression-free survival (PFS) survival curve

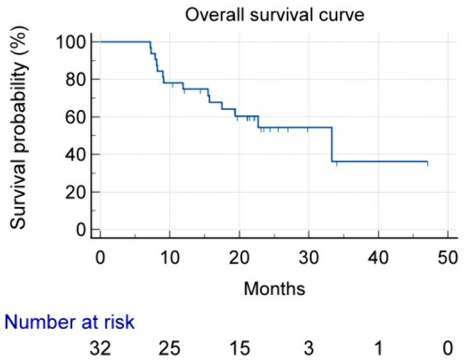

Fig. 3 The Overall survival (OS) survival curve

with TACE in combination with sintilimab and lenvatinib before and after treatment are shown in Fig. 4.

Safety outcomes

A total of 31 patients experienced tr-AEs. Two of the events were classified as grade 3 adverse events, namely hypertension and abdominal pain. Appropriate medications effectively relieved these symptoms. No grade 4 or 5 adverse events occurred. The tr-AEs mainly included hypertension, hand-foot reaction, abdominal pain, diarrhea, and rash. The details are shown in Table 3.

Discussion

In the present study, the combination therapy of TACE with lenvatinib and sintilimab resulted in an impressive ORR of 75.0%, a median PFS of 9.9 months and a median OS of 33.3 months, with tolerable safety profiles. The existing efficacy results demonstrate the potential of this triple therapy to provide survival benefits for patients with uHCC in China when compared to historical data of patients with the same condition.

It is well established that HCC is primarily supplied by the hepatic artery and its growth depends on strong neoarterial vasculogenic activity. There is a complex relationship between angiogenesis and immunity. In the tumor microenvironment, pro-angiogenic factors such as vascular endothelial factor may down-regulate intercellular adhesion molecule 1 (ICAM-1) or vascular cell adhesion protein 1 (VCAM-1), and inhibit T cell movement and dendritic cell (DC) maturation (Kwilas et al. 2015; Kudo et al. 2018; Fu et al. 2021; Peng et al. 2023; Li et al. 2022; Commission and of NH 2022; Marrero et al. 2018; Suzuki et al. 2010). Tumor-derived factors such as vascular endothelial growth factor-A (VEGF-A), interleukin 10 (IL-10) and prostaglandin 2 (PGE2) synergistically induce tumor endothelial cells to express Fas ligand (Fas L). This results in the development of the ability to induce the death of $CD8^+$ T cells, which contributes to the evasion of the immune system by tumors and fosters an immunosuppressive microenvironment in HCC (Motz et al. 2014). VEGF also up-regulates PD-1 expression on T cells, contributing to $CD8^+$ T cell depletion

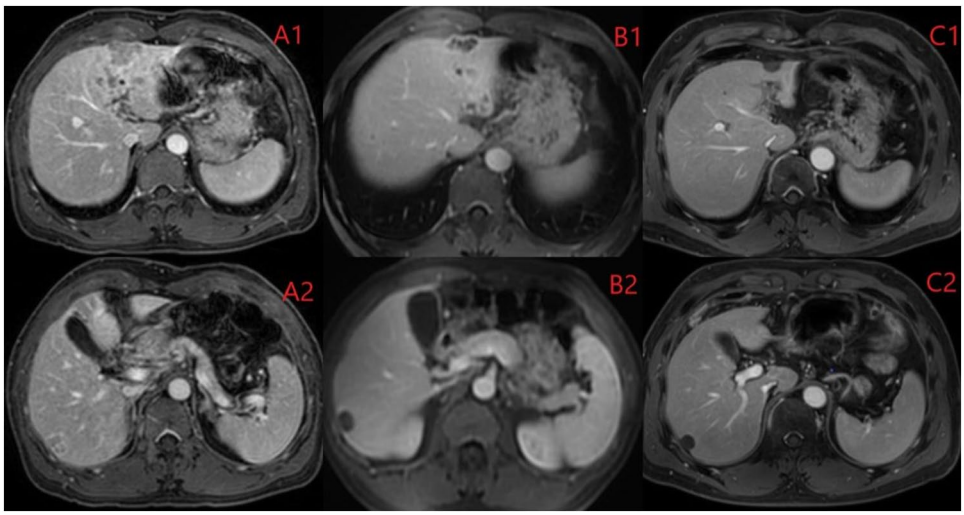

Fig. 4 A1–**C2**) | **A1**, **A2** Imaging manifestations of the patient before the treatment, showing tumors in the left and right lobes of the liver. **B1**, **B2** Imaging manifestations of the patient 6 weeks after TACE, showing tumors in the left and right lobes of the liver with evident necrosis compared with the pretreatment condition. **C1**, **C2** Imaging manifestations of the patient 14 months after TACE, showing tumors in the left and right lobes of the liver were generally necrotic

Table 3 Treatment-related adverse events

Adverse event	Grade 1/2, n (%)	Grade 3, n (%)	Grade 4/5, n (%)
Hypertension	10(31.2)	1(3.1)	0
Hand-foot reaction	8(25.0)	0	0
Skin rash	9(28.1)	0	0
Diarrhea	6(18.8)	0	0
Abdominal pain	5(15.6)	1(3.1)	0
Fatigue	3(9.4)	0	0
Hoarseness	4(12.5)	0	0
Oral herpes	3(9.4)	0	0
Decreased appetite	4(12.5)	0	0
Decreased platelets	1(3.1)	0	0
Decreased white	1(3.1)	0	0
Decreased albumin	2(6.3)	0	0
Hair loss	1(3.1)	0	0
Vomiting	1(3.1)	0	0
Chest tightness	1(3.1)	0	0
Nasal bleeding	1(3.1)	0	0
Bilateral shoulder	1(3.1)	0	0
Back pain	1(3.1)	0	0
Bleeding gums	1(3.1)	0	0
Blisters	1(3.1)	0	0

(Francisco et al. 2010, 2009; Hato et al. 2014). Therefore, it appears that PD-1/PD-L1 inhibitors can enhance the anti-tumor effects of anti-angiogenic medications. In a recent retrospective study (Zhao et al. 2022), it was discovered that patients with HBV-associated advanced HCC who were treated with lenvatinib in combination with sintilimab demonstrated superior PFS and OS as compared with lenvatinib monotherapy. The median PFS was 11.3 months in the combination therapy versus 6.6 months in the lenvatinib monotherapy ($p=0.0128$) and median OS of 21.7 months versus 12.8 months ($p=0.0051$), respectively. In addition, the results of other studies regarding the combination of Tyrosine Kinase Inhibitors (TKIs) with Immune Checkpoint Inhibitors (ICIs) for the treatment of advanced HCC also support the aforementioned theory (Sangro et al. 2021; Finn et al. 2020a, 2020b).

TACE is another effective treatment option in addition to ICI and TKI, for the management of HCC. The most ideal candidates for TACE are patients with intermediate stage HCC. However, it has also been utilized extensively beyond this stage and has become a commonly employed non-surgical treatment option for various stages of HCC due to its effectiveness and widespread availability (Bargellini et al. 2014; Park et al. 2015). The formation of a hypoxic tumor microenvironment after TACE can stimulate the growth of new blood vessels and perhaps attract cells that inhibit the immune system. Therefore, combining TACE with a TKI and/or ICI in triple or dual therapy has demonstrated better therapeutic benefit than a single modality (TACE, TKI or ICI) (Fu et al. 2021; Zhao et al. 2020; Zhu et al. 2021; Yang et al. 2019; Kudo et al. 2020; Chen et al. 2022).

In this study the combination of TACE, sintilimab, and lenvatinib achieved 75.0% ORR, with a median PFS of 9.9 months, and a median OS of 33.3 months. However, in the previous study, the efficacy of TACE combined with lenvatinib and sintilimab in uHCC showed an ORR of 46.7%, with a median PFS of 13.3 months and a median OS of 23.6 months (Cao et al. 2021). Despite utilizing the same combination regimen in both studies, there were variations observed with respect to ORR, PFS and OS. The differences in outcomes may be attributed to variations in baseline characteristics of the patients. In the study, 59.4% of patients had AFP > 400 ng/mL, 43.7% of patients had portal vein invasion, and 37.5% of patients had extrahepatic metastasis. In a previous study, there were 34.6% of patients with AFP > 400 ng/mL and 36.5% of patients with macroscopic vascular invasion (Cao et al. 2021). Furthermore, the limited duration of follow-up time resulted in more than 50% of the patients not experiencing mortality during the follow-up period, potentially accounting for the disparity in the results of OS studies. In addition, due to the short follow-up period, no more than half of the patients met the endpoint during the period, which may explain the variation in OS. Despite the variations between the studies, both demonstrated superior treatment outcomes when compared to the commonly used combination therapy of TKI and ICI for uHCC. However, the advantage in OS still necessitates additional examination (Finn et al. 2020a; Donisi et al. 2020). Findings from another retrospective cohort study also provided evidence supporting the augmented benefits of the triple therapy for patients with HCC (Cai et al. 2022). Compared with the treatment of TACE and lenvatinib, the combination therapy of TACE with lenvatinib and PD-1 inhibitor achieved longer PFS (median 7.3 vs. 4.0 months, $p=0.002$) and OS (median 16.9 vs. 12.1 months, $p=0.009$), and as well as higher objective response rates (56.1% vs. 32.5%, $p=0.033$). It was also discovered that patients may still benefit from repeated TACE during treatment when new lesions appear. At present, there is no standard triple therapy recommended by guidelines, and most of the existing studies are retrospective, with small sample sizes. Prospective, controlled, large-scale studies are required to ascertain whether triple therapy should be the preferred treatment option for patients with uHCC.

In this study, 90.6% of patients experienced tr-AEs, with hypertension being the most prevalent. Two adverse events were classified as Grade 3, however, they were successfully managed through appropriate interventions. Significantly, there were no Grade 4 adverse events. In the previous study with identical treatment regimens (Cai et al. 2022), the

highest incidence of adverse events was malaise, which may due to the high proportion of patients with ECOG PS1. In general, the safety and tolerability of this triple combination approach for treating uHCC was satisfactory compared with other similar studies (Cai et al. 2022; Wu et al. 2021).

This study has various limitations. Initially, the study was conducted retrospectively, which was considered to be of lesser hierarchical value in comparison to prospective investigations. Furthermore, this study was conducted at a single center and utilized a single-arm design, resulting in a restricted sample size. Therefore, large-scale prospective randomized controlled trials are still needed to validate the efficacy and safety of this combination treatment regimen.

Conclusions

The combination therapy of TACE, sintilimab, and lenvatinib has demonstrated a satisfactory effect in the treatment of patients with uHCC in China, with manageable tr-AEs. The encouraging results suggest the potential for applying this combination therapy in clinical settings.

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

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval and consent to participate The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethical approval was waived by the Ethics Committee of the Chinese People's Liberation Army General Hospital. The informed consent was not required for the retrospective nature of the study.

Consent for publication Not applicable.

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