

89995_Auto_Edited.docx

Retrospective Study**Lenvatinib combined with sintilimab plus transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma**

triple therapy as first-line treatment for advanced hepatocellular carcinoma

Sha-Sha Sun, Xiaodi Guo, Wendong Li, Jing-Long Chen

Abstract**BACKGROUND**

Recently, combination therapy has shown a better trend towards improved tumour response and survival outcomes than monotherapy in patients with hepatocellular carcinoma (HCC). However, research on triple therapy [lenvatinib+sintilimab+transarterial chemoembolization (TACE)] as a first-line treatment for advanced HCC is limited.

AIM

To evaluate the safety and efficacy of triple therapy as a first-line treatment for advanced HCC.

METHODS

HCC patients with Barcelona Clinic Liver Cancer stage C treated with triple therapy were enrolled. All patients were treated with lenvatinib every day and sintilimab once every 3 wk. Moreover, TACE was performed every 4-6 wk if necessary. The primary outcome of the study was overall survival (OS). The secondary outcomes were the

objective response rate (ORR), disease control rate (DCR), and incidence of adverse events.

RESULTS

Forty HCC patients who underwent triple therapy were retrospectively analysed from January 2019 to January 2022. With a median follow-up of 8.5 months, the 3-, 6-, and 12-month OS rates were 100%, 88.5%, and 22.5%, respectively. The ORR and DCR were 45% and 90%, respectively. The median PFS and median OS were not reached. Common complications were observed in 76% of the patients (grade 3, 15%; grade 4, 2.5%).

CONCLUSION

Combination therapy comprising lenvatinib, sintilimab and TACE achieved promising outcomes in advanced HCC patients and had manageable effects.

Key Words: lenvatinib, sintilimab, advanced hepatocellular carcinoma; combination therapy; tumor response

Sun SS, Guo X, Li W, Chen JL. Lenvatinib combined with sintilimab plus transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma. *World J Clin Cases* 2023; In press

Core Tip: Currently, advanced hepatocellular carcinoma (HCC) has entered the era of combination therapy. Combination therapy has shown better trend in tumor response and survival outcomes and most combination therapy were dual therapies. The research of triple therapy as first-line treatment for advanced HCC is limited. The purpose of this study was to evaluate the safety and clinical efficacy of triple therapy (lenvatinib+ sintilimab +TACE) in HCC patients with Barcelona Clinic Liver Cancer

(BCLC) stage C. we found triple therapy achieved a promising outcome in advanced HCC patients and had manageable effects.

1 **INTRODUCTION**

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the second leading cause of cancer-related death in China^[1,2]. Due to its occult onset, most HCC patients are diagnosed at an advanced stage and have a poor prognosis^[3]. Currently, systemic therapy [tyrosine kinase inhibitor (TKI) and immune checkpoint inhibitor (ICI)] is a standard treatment recommended by the guidelines for advanced-stage HCC^[3-5]. Recent advances also allow transcatheter arterial chemoembolization (TACE) to be used for the treatment of some advanced-stage patients^[6].

Lenvatinib is an oral small molecule multikinase inhibitor that selectively inhibits tyrosine kinases. The REFLECT trial^[7] revealed that lenvatinib was noninferior to sorafenib in terms of overall survival in patients with untreated advanced hepatocellular carcinoma. The safety and tolerability profiles of lenvatinib were consistent with those previously observed.

Recently, programmed cell death protein-1 (PD-1) inhibitors, including sintilimab, have been used to prolong the overall survival (OS) of unresectable HCC patients. The ORIENT-32 study approved the combination treatment of sintilimab with bevacizumab biosimilar for the treatment of first-line unresectable or metastatic HCC in China^[8].

Although current studies of advanced HCC indicate the promising efficacy of TKIs or PD-1 inhibitors, the objective response rate (ORR) has not been satisfactory. Compared with monotherapy, combination therapy has shown better trends in tumour response and survival outcomes^[9-11]. Moreover, most combination therapies are dual therapies^[12-17]. The efficacy and safety of the relevant triple therapy have been confirmed by real-world data. Cai *et al*^[18] compared TACE combined with lenvatinib plus PD-1 inhibitor (TACE-L-P) versus TACE combined with lenvatinib (TACE-L) for patients with advanced HCC and reported that TACE-L-P significantly improved survival compared with TACE-L, with an acceptable safety profile. A recent review^[19] demonstrated that,

compared with ⁷those in the TACE + Sorafenib group, the OS and median PFS in the TACE + Sorafenib + ICIs group were significantly longer, and the survival rate was significantly improved. However, research ⁸on triple therapy as a first-line treatment for advanced HCC is limited. The purpose of this study was to evaluate the safety and clinical efficacy of triple therapy (lenvatinib+ sintilimab +TACE) in HCC patients with Barcelona Clinic Liver Cancer (BCLC) stage C.

MATERIALS AND METHODS

Patients

A retrospective study was conducted on advanced HCC patients who received triple therapy (lenvatinib+ sintilimab +TACE) between January 2019 and January 2022 at our hospital. Written informed consent was obtained from every patient prior to treatment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The eligibility criteria were as follows: (1) cytological/histological diagnosis by biopsy or two imaging techniques showing typical features of HCC; (2) age 18 to 75 years; (3) Eastern Cooperative Oncology Group performance status of 0-1; (4) Child-Pugh class A or B; (5) BCLC stage C; (6) if it had portal vein tumour thrombus (PVT), the type was Cheng's classification type I or II^[20]; and (7) had not received systemic treatment in the past.

The exclusion criteria were as follows: (1) had severe underlying cardiac or renal disease, oesophageal or gastric variceal bleeding or hepatic encephalopathy, or active infection; (2) a history of other cancers; (3) diffuse liver cancer; and (4) Child-Pugh class C.

Procedures

All patients were treated with lenvatinib every day and sintilimab intravenously once every 3 wk. Moreover, TACE was performed every 4-6 wk if there was obvious hepatic arterial blood supply to the HCC lesion according to contrast-enhanced abdominal magnetic resonance imaging or computed tomography combined with changes in

tumour indicators such as AFP. Patients received 12 mg of lenvatinib orally once a day for bodyweight ≥ 60 kg or 8 mg for bodyweight < 60 kg. Sintilimab (200 mg) was administered intravenously each time. Patients were administered TKIs and PD-1 antibodies within 3 days after the start of TACE.

Follow-up

All patients were regularly followed up every 4 wk through telephone, outpatient visits and WeChat. The tumour response indicators included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) based on the modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria 1.1 [21]. The primary endpoints of this study were the ORR and disease control rate (DCR). The ORR was defined as the proportion of patients who achieved CR or PR and could be maintained for ≥ 4 wk. The DCR was defined as CR, PR or SD. PFS was defined as the time from the first treatment until radiological disease progression or death, whichever occurred first. Overall survival (OS) was assessed from the date of the first treatment until death from any cause. The safety assessments used the Common Terminology Criteria for Adverse Events 4.0 to record adverse events (AEs). The last follow-up date for this study was January 31, 2022.

Statistical analysis

The data were analysed using SPSS for Windows (version 16.0; Chicago, USA). Categorical variables are represented as n. Continuous variables are expressed as medians.

RESULTS

Patient Characteristics

Between January 2019 and January 2022, forty BCLC stage C HCC patients who received triple therapy were included in the study. The median age was 55 years, and approximately 85% of the population was male. There were 30 patients infected with hepatitis B virus who received entecavir. The median diameter of the target lesions was 5.4 cm. Of the 40 patients, 85% had Child–Pugh class A tumours, 55% had multiple

tumours, and 87.5% had unilobar tumours. The baseline characteristics are summarized in Table 1.

Efficacy

The median follow-up was 8.5 months (range, 4–35 months). Eighteen patients underwent one session of TACE, and the other 22 patients received two or more sessions of TACE. Each patient received ≥ 3 anti-PD-1 antibody injection cycles. The median duration of TKI administration was 8 months. The median PFS and median OS were not reached. The 3-, 6-, and 12-month OS rates were 100%, 88.5%, and 22.5%, respectively. In total, 12.5% (5/40) of the HCC patients achieved CR, and 32.5% (13/40) achieved PR after combination therapy. The ORR was 45%, and the DCR was 90% (Table 2). The ORR of the Child–Pugh B group reached 7.5%, while that of the Child–Pugh A group was 37.5%.

Safety

No grade 5 treatment-related AEs occurred in the population. Only one patient had grade 4 AE of autoimmune haemolytic anaemia, which was relieved after the application of glucocorticoids. Common complications, including fever, pain, fatigue, anorexia, hypertension, hand-foot skin reaction, transient liver function injury, leukocytopenia and thrombocytopenia, were observed in most patients (Table 3). Most AEs were mild or moderate and could be improved after symptomatic treatment.

DISCUSSION

Our study retrospectively analysed clinical data from 40 HCC patients with BCLC stage C disease who underwent combination treatment comprising lenvatinib+ sintilimab +TACE. It was found that triple therapy was associated with a higher response rate and tolerable adverse effects.

HCC is a serious global health problem because current treatments have limited efficacy for treating HCC patients, especially those with advanced-stage HCC. To date, the first-line treatments for advanced HCC include sorafenib, lenvatinib, carrilizumab combined with apatinib, donafenib and atezolizumab plus bevacizumab. Sorafenib is an oral

multikinase inhibitor that can prolong OS by approximately 3 months for advanced HCC patients compared with that of patients treated with a placebo^[22, 23]. Lenvatinib is another oral TKI that can block vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor α , RET, and KIT^[24]. Lenvatinib successfully improved survival compared with sorafenib in a phase III trial, with an ORR of 24.1%^[7, 25]. Although lenvatinib has significant improvement in OS, its effects are not easily sustained.

With the successful application of anti-PD-1 therapy in melanoma^[26], numerous studies are currently exploring the use of anti-PD-1 monoclonal antibodies (mAbs) for the treatment of HCC. Anti-PD-1 mAbs such as pembrolizumab and nivolumab could halt malignant cell growth and activate T cells to recognize and attack cancer cells^[27, 28]. A multicentre, phase I/II, open-label trial investigating nivolumab in sorafenib-pretreated patients showed objective outcomes, with an ORR of 15% and a median OS of 15.6 months^[29]. Pembrolizumab was also used to treat sorafenib-resistant patients, with promising results, namely, 4.9-month PFS, 12.9-month OS and 17% ORR^[9]. Currently, sintilimab is the first and only PD-1 inhibitor approved for this purpose in China. Many studies have demonstrated the promising efficacy of anti-PD-1 therapy in patients with advanced HCC, yet the ORR has not been satisfactory.

TACE is a standard treatment for intermediate-stage HCC^[30]. Currently, a few studies suggest that TACE be considered when treating advanced HCC patients with segmental portal vein tumour thrombosis (PVTT) and preserved liver function^[6]. Moreover, TACE activates the host immune system by promoting local inflammation and triggering the release of tumour antigens^[31].

Recently, combination therapy has shown better trends in tumour response and survival than monotherapy. TKIs affect immune effectors, antigen presentation and the tumoral microenvironment, possibly by dampening or augmenting the immune response to cancer^[32]. Therefore, numerous studies are exploring the combination treatment of TKIs plus ICIs in advanced-stage HCC. A phase Ib study analysing the association of lenvatinib with pembrolizumab in first-line therapy for advanced HCC

[12] indicated an ORR of 42.3% and a median PFS of 9.69 months. In 2020, the combination regimen of bevacizumab plus atezolizumab was approved by the FDA as a first-line treatment for unresectable HCC based on the results of the IMbrave150 trial^[33]. Many studies have ^[19, 34, 35] shown that the DCR and OS are greater in the TACE+TKI+ICIs group than in the TACE+TKI group, TKI+ICIs group or TACE+TKI group.

Thus, this study investigated combination therapy comprising lenvatinib+ sintilimab + TACE, which achieved a higher tumour response. The ORR and DCR were 45% and 90%, respectively. Due to the different study populations, our outcomes were different from those of the other studies (ORR: 77.4%, DCR: 91.9%), which focused on the combination of TKIs, PD-1 inhibitors and TACE in unresectable HCC patients^[36]. That trial included patients with BCLC stages A, B and C. However, our study enrolled only patients with BCLC stage C disease. Notably, 15% of the selected population had Child–Pugh B disease, which was different from the findings of previous studies, which included Child–Pugh A patients. The ORR of the Child–Pugh B group was lower than that of the Child–Pugh A group. On the one hand, the combination strategy could be applied appropriately in the Child–Pugh B population. However, additional clinical studies are needed for verification. On the other hand, the outcome suggested that advanced HCC patients with Child–Pugh A could achieve a high tumour response rate when treated with triple therapy comprising TKI+PD-1+TACE. A retrospective study ^[18] demonstrated that TACE combined with lenvatinib plus a PD-1 inhibitor significantly improved survival compared with TACE combined with lenvatinib, with an acceptable safety profile in advanced HCC patients. TACE combined with antiangiogenic-targeted therapy and immune checkpoint inhibitors^[37] may have promising anticancer effects on unresectable HCC patients with PVTT, and the ORR and DCR were 48.7% and 84.6%, respectively. A retrospective analysis ^[38] of 34 HCC patients who received TACE and camrelizumab revealed that the ORR was 35.3%, and the median OS was 13.3 months.

There was no treatment-related death observed in the group. Hypertension, hand-foot skin reaction, fatigue and proteinuria are likely associated with lenvatinib. There was a greater incidence of pain, fever, liver dysfunction, nausea and vomiting, which might be linked to TACE. The development of thyroid dysfunction and autoimmune haemolytic anaemia might be linked to sintilimab. Most treatment-related AEs were mild and controllable. These findings are similar to previous reports^[36, 39].

11 This study has several limitations. First, this was a retrospective single-center study, which inevitably leads to selection bias. Thus, multicentre prospective studies are needed. Second, the sample size was small. Therefore, it is necessary to expand the sample size to reduce bias.

CONCLUSION

6 Overall, the combination therapy of lenvatinib, sintilimab and TACE was associated with a high rate of tumour response in patients with advanced HCC, and had manageable toxicity. Given the short follow-up period, additional clinical trials are needed to confirm the efficacy of the triple therapy strategy.

ARTICLE HIGHLIGHTS

Research background

2 HCC is a serious global health problem because current treatments have limited efficacy for treating HCC patients, especially those with advanced- stage HCC. Recently, combination therapy has shown better trends in tumour response and survival than monotherapy. However, research on triple therapy [lenvatinib+sintilimab+ transarterial chemoembolization (TACE)] as a first-line treatment for advanced HCC is limited.

Research motivation

Although current studies of advanced HCC indicate promising efficiency of TKIs or PD-1 inhibitors, the objective response rate remains unsatisfactory.

Research objectives

The study evaluated the safety and clinical efficacy of triple therapy in HCC patients with BCLC stage C.

Research methods

The primary outcome of the study was overall survival (OS). The secondary outcomes were the objective response rate (ORR), disease control rate (DCR), and incidence of adverse events.

Research results

The ORR and DCR were 45% and 90%, respectively. Common complications were observed in 76% of the patients (grade 3, 15%; grade 4, 2.5%).

Research conclusions

Combination therapy comprising lenvatinib, sintilimab and TACE achieved promising outcomes in advanced HCC patients and had manageable effects.

Research perspectives

More multicentre prospective studies are needed.

16%

SIMILARITY INDEX

PRIMARY SOURCES

- | | | |
|----------|---|----------------------|
| 1 | f6publishing.blob.core.windows.net
<small>Internet</small> | 86 words — 3% |
| <hr/> | | |
| 2 | www.ncbi.nlm.nih.gov
<small>Internet</small> | 69 words — 3% |
| <hr/> | | |
| 3 | www.researchgate.net
<small>Internet</small> | 60 words — 2% |
| <hr/> | | |
| 4 | www.frontiersin.org
<small>Internet</small> | 54 words — 2% |
| <hr/> | | |
| 5 | jitc.biomedcentral.com
<small>Internet</small> | 22 words — 1% |
| <hr/> | | |
| 6 | "Abstracts of the 26th Annual Conference of APASL, February 15–19, 2017, Shanghai, China", Hepatology International, 2017
<small>Crossref</small> | 21 words — 1% |
| <hr/> | | |
| 7 | Haoer Jin, Sha Qin, Jiang He, Juxiong Xiao, Qingling Li, Yitao Mao, Luqing Zhao. "New insights into checkpoint inhibitor immunotherapy and its combined therapies in hepatocellular carcinoma: from mechanisms to clinical trials", International Journal of Biological Sciences, 2022
<small>Crossref</small> | 20 words — 1% |

8 Jia-Yi Wu, Zhen-Yu Yin, Yan-Nan Bai, Yu-Feng Chen et al. "Lenvatinib Combined with Anti-PD-1 Antibodies Plus Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: A Multicenter Retrospective Study", Journal of Hepatocellular Carcinoma, 2021 20 words — 1%

[Crossref](#)

9 Claudia Angela Maria Fulgenzi, Antonio D'Alessio, Thomas Talbot, Alessandra Gennari et al. "New Frontiers in the Medical Therapy of Hepatocellular Carcinoma", Chemotherapy, 2022 19 words — 1%

[Crossref](#)

10 Ting Zhou, Xintian Wang, Yingdan Cao, Lan Yang, Zijing Wang, Aixia Ma, Hongchao Li. "Cost-effectiveness analysis of sintilimab plus bevacizumab biosimilar compared with lenvatinib as the first-line treatment of unresectable or metastatic hepatocellular carcinoma", BMC Health Services Research, 2022 18 words — 1%

[Crossref](#)

11 Jianbo Guo, Lei Zhang, Liping Zhang, Junqi Wu et al. "The additional radiotherapy to adjuvant chemotherapy improves the prognosis of stage III-N2 with highest mediastinal lymph node metastasis in non-small cell lung cancer", Journal of Cancer Research and Clinical Oncology, 2023 15 words — 1%

[Crossref](#)

12 Min Kyung Park, Yun Bin Lee, Hyemi Moon, Na Ryung Choi et al. "Effectiveness of Lenvatinib Versus Sorafenib for Unresectable Hepatocellular Carcinoma in Patients with Hepatic Decompensation", Digestive Diseases and Sciences, 2022 15 words — 1%

[Crossref](#)

13 Yujing Xin, Fei Cao, Hongcai Yang, Xinyuan Zhang, Yi Chen, Xiaojing Cao, Xiang Zhou, Xiao Li, Jinxue Zhou. "Efficacy and safety of atezolizumab plus bevacizumab combined with hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma", Frontiers in Immunology, 2022 14 words — 1%
Crossref

14 encyclopedia.pub 14 words — 1%
Internet

EXCLUDE QUOTES ON
EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES < 1%
EXCLUDE MATCHES < 10 WORDS