ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2024 January 16; 12(2): 236-465

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 12 Number 2 January 16, 2024

EDITORIAL

ORIGINAL ARTICLE

Retrospective Study

Observational Study

Randomized Controlled Trial

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 2 January 16, 2024

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 2 January 16, 2024

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 12 Number 2 January 16, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Xin Ye, MD, Professor, Department of Oncology, The First Affiliated Hospital of Shandong First Medical University, Jinan 250014, Shandong Province, China. yexintaian2020@163.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
January 16, 2024

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2024 January 16; 12(2): 285-292

DOI: 10.12998/wjcc.v12.i2.285

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Retrospective Study

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

Sha-Sha Sun, Xiao-Di Guo, Wen-Dong Li, Jing-Long Chen

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Join-Lambert O, France

Received: November 20, 2023
Peer-review started: November 20, 2023
First decision: December 5, 2023
Revised: December 13, 2023
Accepted: December 27, 2023
Article in press: December 27, 2023
Published online: January 16, 2024

Sha-Sha Sun, Xiao-Di Guo, Wen-Dong Li, Jing-Long Chen, Department of Oncology, Capital Medical University Affiliated Beijing Ditan Hospital, Beijing 100015, China

Corresponding author: Jing-Long Chen, MS, Associate Professor, Department of Oncology, Capital Medical University Affiliated Beijing Ditan Hospital, No. 8 Jingshun East Street, Chaoyang District, Beijing 100015, China. hhh540027@126.com

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-mo OS rates were 100%, 88.5%, and 22.5%, respectively. The ORR and DCR were 45% and 90%, respectively. The median progressive free survival 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

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 + transarterial chemoembolization) in HCC patients with Barcelona Clinic Liver Cancer stage C. We found triple therapy achieved a promising outcome in advanced HCC patients and had manageable effects.

Citation: Sun SS, Guo XD, Li WD, Chen JL. Lenvatinib combined with sintilimab plus transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma. *World J Clin Cases* 2024; 12(2): 285-292
URL: https://www.wjgnet.com/2307-8960/full/v12/i2/285.htm
DOI: https://dx.doi.org/10.12998/wjcc.v12.i2.285

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 (OS) in patients with untreated advanced HCC. 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 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) *vs* 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 those in the TACE + Sorafenib group, the OS and median progressive free survival (PFS) in the TACE + Sorafenib + ICIs group were significantly longer, and the survival rate was significantly improved. However, research on 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 (PVTT), 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 alpha-fetoprotein. Patients received 12 mg of lenvatinib orally once a day for body weight ≥ 60 kg or 8 mg for body weight < 60 kg. Sintilimab (200 mg) was administered intravenously each time. Patients were administered TKIs and PD-1 antibodies within 3 d 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 based on the modified Response Evaluation Criteria in Solid Tumours 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. 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 (AEs) 4.0 to record 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, United States). 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 mo (range, 4–35 mo). 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-mo 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 mo 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

Table 1 Baseline characteristics for patients, *n* (%)

Variables	Patients (*n* = 40)
Sex	
Male	34 (85)
Female	6 (15)
Age, yr	55 ± 9
HBsAg	
Positive	30 (75)
Negative	10 (25)
Alb (g/L)	38.7 ± 4.7
AFP (ng/mL)	
< 400	26 (65)
≥ 400	14 (35)
Child-Pugh class	
A	34 (85)
B	6 (15)
Tumor-number	
Solitary	18 (45)
Multiple	22 (55)
Max-diameter (cm)	5.4 ± 3.3
Extrahepatic metastasis	14 (35)
PVTT	
Left	6 (15)
Right	23 (57.5)
None	11 (27.5)
Tumor distribution	
Uni-lobar	35 (87.5)
Bi-lobar	5 (12.5)

HBsAg: Hepatitis B surface antigen; ALB: Albumin; AFP: Alpha fetoprotein; PVTT: Portal vein tumor thrombus.

Table 2 Tumor best response, *n* (%)

Response	Patients (*n* = 40)
CR	5 (12.5)
PR	13 (32.5)
SD	18 (45)
PD	4 (10)
ORR	18 (45)
DCR	36 (90)

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; ORR: Objective response rate; DCR: Disease control rate.

Table 3 common treatment-related adverse events, *n* (%)

Adverse events	Grade 1/2	Grade 3/4	Any grade
Fatigue	13 (32.5)	0	13 (32.5)
Anorexia	5 (12.5)	0	5 (12.5)
Leukocytopenia	15 (37.5)	0	15 (37.5)
Increased alanine aminotransferase	27 (67.5)	1 (2.5)	28 (70)
Increased aspartate aminotransferase	24 (60)	1 (2.5)	25 (62.5)
Thrombocytopenia	9 (22.5)	1 (2.5)	10 (25)
Hypertension	12 (30)	0	12 (30)
Hand-foot skin reaction	13 (32.5)	2 (5)	15 (37.5)
Diarrhea	3 (7.5)	0	3 (7.5)
Hypothyroidism	5 (12.5)	0	5 (12.5)
Hyperthyroidism	1 (2.5)	0	1 (2.5)
Emaciation	6 (15)	0	6 (15)
Fever	10 (12.5)	0	10 (12.5)
Pain	19 (47.5)	0	19 (47.5)
Proteinuria	3 (7.5)	1 (2.5)	4 (10)
Elevated bilirubin	5 (12.5)	0	5 (12.5)
Autoimmune hemolytic anemia	0	1 (2.5)	1 (2.5)

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 mo[29]. Pembrolizumab was also used to treat sorafenib-resistant patients, with promising results, namely, 4.9-mo PFS, 12.9-mo 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 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 mo. 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 mo.

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].

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

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

Hepatocellular carcinoma (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 tyrosine kinase inhibitors or death protein-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 Barcelona Clinic Liver Cancer stage C.

Research methods

The primary outcome of the study was overall survival. 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.

FOOTNOTES

Author contributions: Sun SS and Chen JL designed the experiment; Sun SS and Guo XD collected the data; Guo XD and Li WD analysed data; Sun SS and Chen JL wrote and revised the manuscript.

Supported by Capital Health Development and Scientific Research Special Project, No. 2022-2-2175.

Institutional review board statement: The study was reviewed and approved by Beijing Ditan Hospital Affiliated to Capital Medical University Institutional Review Board (Approval No. 014-01).

Informed consent statement: Written informed consent was obtained from every patient prior to treatment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Sha-Sha Sun 0000-0001-8564-4603; Jing-Long Chen 0000-0003-0641-5672.

S-Editor: Li L
L-Editor: A
P-Editor: Li L

REFERENCES

1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
2 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]
3 **Villanueva A**. Hepatocellular Carcinoma. *N Engl J Med* 2019; **380**: 1450-1462 [PMID: 30970190 DOI: 10.1056/NEJMra1713263]
4 **Xie DY**, Ren ZG, Zhou J, Fan J, Gao Q. 2019 Chinese clinical guidelines for the management of hepatocellular carcinoma: updates and insights. *Hepatobiliary Surg Nutr* 2020; **9**: 452-463 [PMID: 32832496 DOI: 10.21037/hbsn-20-480]
5 **Yang JD**, Heimbach JK. New advances in the diagnosis and management of hepatocellular carcinoma. *BMJ* 2020; **371**: m3544 [PMID: 33106289 DOI: 10.1136/bmj.m3544]
6 **Chang Y**, Jeong SW, Young Jang J, Jae Kim Y. Recent Updates of Transarterial Chemoembololization in Hepatocellular Carcinoma. *Int J Mol Sci* 2020; **21** [PMID: 33142892 DOI: 10.3390/ijms21218165]
7 **Kudo M**, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, Baron A, Park JW, Han G, Jassem J, Blanc JF, Vogel A, Komov D, Evans TRJ, Lopez C, Dutcus C, Guo M, Saito K, Kraljevic S, Tamai T, Ren M, Cheng AL. Lenvatinib *vs* sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018; **391**: 1163-1173 [PMID: 29433850 DOI: 10.1016/S0140-6736(18)30207-1]
8 **Ren Z**, Xu J, Bai Y, Xu A, Cang S, Du C, Li Q, Lu Y, Chen Y, Guo Y, Chen Z, Liu B, Jia W, Wu J, Wang J, Shao G, Zhang B, Shan Y, Meng Z, Gu S, Yang W, Liu C, Shi X, Gao Z, Yin T, Cui J, Huang M, Xing B, Mao Y, Teng G, Qin Y, Xia F, Yin G, Yang Y, Chen M, Wang Y, Zhou H, Fan J; ORIENT-32 study group. Sintilimab plus a bevacizumab biosimilar (IBI305) *vs* sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. *Lancet Oncol* 2021; **22**: 977-990 [PMID: 34143971 DOI: 10.1016/S1470-2045(21)00252-7]
9 **Luo XY**, Wu KM, He XX. Advances in drug development for hepatocellular carcinoma: clinical trials and potential therapeutic targets. *J Exp Clin Cancer Res* 2021; **40**: 172 [PMID: 34006331 DOI: 10.1186/s13046-021-01968-w]
10 **Mei J**, Tang YH, Wei W, Shi M, Zheng L, Li SH, Guo RP. Hepatic Arterial Infusion Chemotherapy Combined With PD-1 Inhibitors Plus Lenvatinib Versus PD-1 Inhibitors Plus Lenvatinib for Advanced Hepatocellular Carcinoma. *Front Oncol* 2021; **11**: 618206 [PMID: 33718175 DOI: 10.3389/fonc.2021.618206]
11 **Liu Z**, Lin Y, Zhang J, Zhang Y, Li Y, Liu Z, Li Q, Luo M, Liang R, Ye J. Molecular targeted and immune checkpoint therapy for advanced hepatocellular carcinoma. *J Exp Clin Cancer Res* 2019; **38**: 447 [PMID: 31684985 DOI: 10.1186/s13046-019-1412-8]
12 **Finn RS**, Ikeda M, Zhu AX, Sung MW, Baron AD, Kudo M, Okusaka T, Kobayashi M, Kumada H, Kaneko S, Pracht M, Mamontov K, Meyer T, Kubota T, Dutcus CE, Saito K, Siegel AB, Dubrovsky L, Mody K, Llovet JM. Phase Ib Study of Lenvatinib Plus Pembrolizumab in Patients With Unresectable Hepatocellular Carcinoma. *J Clin Oncol* 2020; **38**: 2960-2970 [PMID: 32716739 DOI: 10.1200/JCO.20.00808]
13 **Cheng Z**, He L, Guo Y, Song Y, Song S, Zhang L. The combination therapy of transarterial chemoembolisation and sorafenib is the preferred palliative treatment for advanced hepatocellular carcinoma patients: a meta-analysis. *World J Surg Oncol* 2020; **18**: 243 [PMID: 32917226 DOI: 10.1186/s12957-020-02017-0]
14 **Xu J**, Shen J, Gu S, Zhang Y, Wu L, Wu J, Shao G, Xu L, Yin T, Liu J, Ren Z, Xiong J, Mao X, Zhang L, Yang J, Li L, Chen X, Wang Z, Gu K, Pan Z, Ma K, Zhou X, Yu Z, Li E, Yin G, Zhang X, Wang S, Wang Q. Camrelizumab in Combination with Apatinib in Patients with Advanced Hepatocellular Carcinoma (RESCUE): A Nonrandomized, Open-label, Phase II Trial. *Clin Cancer Res* 2021; **27**: 1003-1011 [PMID: 33087333 DOI: 10.1158/1078-0432.CCR-20-2571]
15 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]
16 **Cheng H**, Sun G, Chen H, Li Y, Han Z, Zhang P, Yang L. Trends in the treatment of advanced hepatocellular carcinoma: immune checkpoint blockade immunotherapy and related combination therapies. *Am J Cancer Res* 2019; **9**: 1536-1545 [PMID: 31497341]
17 **Yau T**, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou MM, Matilla A, Tovoli F, Knox JJ, Ruth He A, El-Rayes BF, Acosta-Rivera M, Lim HY, Neely J, Shen Y, Wisniewski T, Anderson J, Hsu C. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients With Advanced Hepatocellular Carcinoma Previously Treated With Sorafenib: The CheckMate 040 Randomized Clinical Trial. *JAMA Oncol* 2020; **6**: e204564 [PMID: 33001135 DOI: 10.1001/jamaoncol.2020.4564]
18 **Cai M**, Huang W, Huang J, Shi W, Guo Y, Liang L, Zhou J, Lin L, Cao B, Chen Y, Zhu K. Transarterial Chemoembolization Combined With

Lenvatinib Plus PD-1 Inhibitor for Advanced Hepatocellular Carcinoma: A Retrospective Cohort Study. *Front Immunol* 2022; **13**: 848387 [PMID: 35300325 DOI: 10.3389/fimmu.2022.848387]

19 **Zheng L**, Fang S, Wu F, Chen W, Chen M, Weng Q, Wu X, Song J, Zhao Z, Ji J. Efficacy and Safety of TACE Combined With Sorafenib Plus Immune Checkpoint Inhibitors for the Treatment of Intermediate and Advanced TACE-Refractory Hepatocellular Carcinoma: A Retrospective Study. *Front Mol Biosci* 2020; **7**: 609322 [PMID: 33521054 DOI: 10.3389/fmolb.2020.609322]

20 **Cheng S**, Chen M, Cai J, Sun J, Guo R, Bi X, Lau WY, Wu M. Chinese Expert Consensus on Multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2018 Edition). *Liver Cancer* 2020; **9**: 28-40 [PMID: 32071907 DOI: 10.1159/000503685]

21 **Llovet JM**, Lencioni R. mRECIST for HCC: Performance and novel refinements. *J Hepatol* 2020; **72**: 288-306 [PMID: 31954493 DOI: 10.1016/j.jhep.2019.09.026]

22 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

23 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

24 **Yamamoto Y**, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, Tohyama O, Semba T, Yamaguchi A, Hoshi SS, Mimura F, Haneda T, Fukuda Y, Kamata JI, Takahashi K, Matsukura M, Wakabayashi T, Asada M, Nomoto KI, Watanabe T, Dezso Z, Yoshimatsu K, Funahashi Y, Tsuruoka A. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. *Vasc Cell* 2014; **6**: 18 [PMID: 25197551 DOI: 10.1186/2045-824X-6-18]

25 **Pinter M**, Peck-Radosavljevic M. Review article: systemic treatment of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2018; **48**: 598-609 [PMID: 30039640 DOI: 10.1111/apt.14913]

26 **Hamid O**, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, Joseph RW, Weber JS, Dronca R, Gangadhar TC, Patnaik A, Zarour H, Joshua AM, Gergich K, Elassaiss-Schaap J, Algazi A, Mateus C, Boasberg P, Tumeh PC, Chmielowski B, Ebbinghaus SW, Li XN, Kang SP, Ribas A. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013; **369**: 134-144 [PMID: 23724846 DOI: 10.1056/NEJMoa1305133]

27 **Park R**, Eshrat F, Al-Jumayli M, Saeed A. Immuno-Oncotherapeutic Approaches in Advanced Hepatocellular Carcinoma. *Vaccines (Basel)* 2020; **8** [PMID: 32784389 DOI: 10.3390/vaccines8030447]

28 **Leone P**, Solimando AG, Fasano R, Argentiero A, Malerba E, Buonavoglia A, Lupo LG, De Re V, Silvestris N, Racanelli V. The Evolving Role of Immune Checkpoint Inhibitors in Hepatocellular Carcinoma Treatment. *Vaccines (Basel)* 2021; **9** [PMID: 34065489 DOI: 10.3390/vaccines9050532]

29 **El-Khoueiry AB**, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, Kim TY, Choo SP, Trojan J, Welling TH Rd, Meyer T, Kang YK, Yeo W, Chopra A, Anderson J, Dela Cruz C, Lang L, Neely J, Tang H, Dastani HB, Melero I. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet* 2017; **389**: 2492-2502 [PMID: 28434648 DOI: 10.1016/S0140-6736(17)31046-2]

30 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]

31 **Kudo M**. Immuno-Oncology Therapy for Hepatocellular Carcinoma: Current Status and Ongoing Trials. *Liver Cancer* 2019; **8**: 221-238 [PMID: 31602367 DOI: 10.1159/000501501]

32 **Harding JJ**, El Dika I, Abou-Alfa GK. Immunotherapy in hepatocellular carcinoma: Primed to make a difference? *Cancer* 2016; **122**: 367-377 [PMID: 26540029 DOI: 10.1002/cncr.29769]

33 **Casak SJ**, Donoghue M, Fashoyin-Aje L, Jiang X, Rodriguez L, Shen YL, Xu Y, Liu J, Zhao H, Pierce WF, Mehta S, Goldberg KB, Theoret MR, Kluetz PG, Pazdur R, Lemery SJ. FDA Approval Summary: Atezolizumab Plus Bevacizumab for the Treatment of Patients with Advanced Unresectable or Metastatic Hepatocellular Carcinoma. *Clin Cancer Res* 2021; **27**: 1836-1841 [PMID: 33139264 DOI: 10.1158/1078-0432.CCR-20-3407]

34 **Huang JT**, Zhong BY, Jiang N, Li WC, Zhang S, Yin Y, Yang J, Shen J, Wang WS, Zhu XL. Transarterial Chemoembolization Combined with Immune Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors *vs* Immune Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors for Advanced Hepatocellular Carcinoma. *J Hepatocell Carcinoma* 2022; **9**: 1217-1228 [PMID: 36474670 DOI: 10.2147/JHC.S386672]

35 **Han Z**, Yang F, Zhang Y, Wang J, Ni Q, Zhu H, Zhou X, Gao H, Lu J. Prognostic efficacy and prognostic factors of TACE plus TKI with ICIs for the treatment of unresectable hepatocellular carcinoma: A retrospective study. *Front Oncol* 2022; **12**: 1029951 [PMID: 36591442 DOI: 10.3389/fonc.2022.1029951]

36 **Wu JY**, Yin ZY, Bai YN, Chen YF, Zhou SQ, Wang SJ, Zhou JY, Li YN, Qiu FN, Li B, Yan ML. Lenvatinib Combined with Anti-PD-1 Antibodies Plus Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: A Multicenter Retrospective Study. *J Hepatocell Carcinoma* 2021; **8**: 1233-1240 [PMID: 34676181 DOI: 10.2147/JHC.S332420]

37 **Feng JK**, Liu ZH, Fu ZG, Chai ZT, Sun JX, Wang K, Cheng YQ, Zhu HF, Xiang YJ, Zhou LP, Shi J, Guo WX, Zhai J, Cheng SQ. Efficacy and safety of transarterial chemoembolization plus antiangiogenic- targeted therapy and immune checkpoint inhibitors for unresectable hepatocellular carcinoma with portal vein tumor thrombus in the real world. *Front Oncol* 2022; **12**: 954203 [PMID: 36505818 DOI: 10.3389/fonc.2022.954203]

38 **Zhang JX**, Chen P, Liu S, Zu QQ, Shi HB, Zhou CG. Safety and Efficacy of Transarterial Chemoembolization and Immune Checkpoint Inhibition with Camrelizumab for Treatment of Unresectable Hepatocellular Carcinoma. *J Hepatocell Carcinoma* 2022; **9**: 265-272 [PMID: 35388358 DOI: 10.2147/JHC.S358658]

39 **Chen J**, Hu X, Li Q, Dai W, Cheng X, Huang W, Yu W, Chen M, Guo Y, Yuan G. Effectiveness and safety of toripalimab, camrelizumab, and sintilimab in a real-world cohort of hepatitis B virus associated hepatocellular carcinoma patients. *Ann Transl Med* 2020; **8**: 1187 [PMID: 33241036 DOI: 10.21037/atm-20-6063]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com