ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2020 July 21; 26(27): 3851-3997

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 26 Number 27 July 21, 2020

GUIDELINES

REVIEW

MINIREVEIWS

ORIGINAL ARTICLE

Basic Study

Retrospective Study

Observational Study

ABOUT COVER

Amedeo Amedei graduated in Biology at Florence University in 1996. He started his scientific career studying the role of Th1/Th2 lymphocytes in GVHD, atopic dermatitis and kidney rejection. In 2003 began his doctor´s degree in "Clinical and Sperimental Medicine". In 2005, he became researcher at Department of Experimental and Clinical Medicine (University of Florence), where in 2015 he was appointed Associate Professor. Recently, Prof. Amedei has focused his scientific interests on the cancer immunology and the role of microbiome. The great quality of his international profile is documented by scientific production: 144 peer reviewed articles (7056 citations, h-index: 43.04), 8 book chapters and one patent. Prof. Amedei is serving as an Editorial Board member of 30 international journals, as referee of 43 journal, as Co-Editor-Chief and carries out activities as scientific reviewer for international research projects of private and public entities. From 2016 he is in the Scientific Council of "Toscana Life Sciences ".

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2020 edition of Journal Citation Report® cites the 2019 impact factor (IF) for *WJG* as 3.665; IF without journal self cites: 3.534; 5-year IF: 4.048; Ranking: 35 among 88 journals in gastroenterology and hepatology; and Quartile category: Q2.

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS
http://www.wjgnet.com/1007-9327/editorialboard.htm

PUBLICATION DATE
July 21, 2020

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

E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Gastroenterology

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

World J Gastroenterol 2020 July 21; 26(27): 3975-3988

DOI: 10.3748/wjg.v26.i27.3975

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Transarterial chemoembolization with hepatic arterial infusion chemotherapy plus S-1 for hepatocellular carcinoma

Jian-Hai Guo, Shao-Xing Liu, Song Gao, Fu-Xin Kou, Xin Zhang, Di Wu, Xiao-Ting Li, Hui Chen, Xiao-Dong Wang, Peng Liu, Peng-Jun Zhang, Hai-Feng Xu, Guang Cao, Lin-Zhong Zhu, Ren-Jie Yang, Xu Zhu

ORCID number: Jian-Hai Guo 0000-0001-6700-0978; Shao-Xing Liu 0000-0003-0444-9158; Song Gao 0000-0002-7466-3654; Fu-Xin Kou 0000-0003-4139-8943; Xin Zhang 0000-0001-9035-1442; Di Wu 0000-0002-0419-6552; Xiao-Ting Li 0000-0001-5191-5815; Hui Chen 0000-0001-8541-2167; Xiao-Dong Wang 0000-0003-1013-9308; Peng Liu 0000-0002-3809-6023; Peng-Jun Zhang 0000-0002-7391-2495; Hai-Feng Xu 0000-0003-0023-3894; Guang Cao 0000-0002-8978-4053; Lin-Zhong Zhu 0000-0003-3195-5785; Ren-Jie Yang 0000-0002-9954-4395; Xu Zhu 0000-0001-9983-5048.

Author contributions: Guo JH, Liu SX and Gao S contributed equally and were responsible for the study conception and design, study conduction, data analysis and interpretation, and manuscript drafting; Kou FX, Zhang X, Chen H, Wang XD, Liu P, Zhang PJ, Xu HF, Cao G and Zhu LZ were responsible for study conduction and data collection; Wu D and Li XT were responsible for data analysis and interpretation; Yang PJ and Zhu X revised the article for important intellectual content; all authors reviewed and approved the final version to be published.

Supported by Sanofi.

Institutional review board

Jian-Hai Guo, Shao-Xing Liu, Song Gao, Fu-Xin Kou, Xin Zhang, Di Wu, Hui Chen, Xiao-Dong Wang, Peng Liu, Peng-Jun Zhang, Hai-Feng Xu, Guang Cao, Lin-Zhong Zhu, Ren-Jie Yang, Xu Zhu, Department of Interventional Therapy, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing 100142, China

Xiao-Ting Li, Department of Radiology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing 100142, China

Corresponding author: Xu Zhu, MD, Chief Doctor, Professor, Department of Interventional Therapy, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, No. 52, Fucheng Road, Haidian District, Beijing 100142, China. drzhuxu@163.com

Abstract

BACKGROUND

Transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) have shown promising local benefits for advanced hepatocellular carcinoma (HCC). S-1, a composite preparation of a 5-fluorouracil prodrug, has proven to be a convenient oral chemotherapeutic agent with definite efficacy against advanced HCC.

AIM

To evaluate the efficacy and safety of TACE followed by HAIC with or without oral S-1 for treating advanced HCC.

METHODS

In this single-center, open-label, prospective, randomized controlled trial, 117 participants with advanced HCC were randomized to receive TACE followed by oxaliplatin-based HAIC either with (TACE/HAIC + S-1, n = 56) or without (TACE/HAIC, n = 61) oral S-1 between December 2013 and September 2017. Two participants were excluded from final analysis for withdrawing consent. The primary endpoint was progression-free survival (PFS) and secondary endpoints included overall survival (OS), objective response rate, disease control rate and

statement: The study was reviewed and approved by the Peking University Cancer Hospital Institutional Review Board.

Clinical trial registration statement: The study was registered at ClinicalTrials.gov. The registration identification number is NCT01997957.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Guo JH, Liu SX, Gao S, Kou FX, Zhang X, Chen H, Wang XD, Liu P, Xu HF, Cao G, Zhu LZ, Yang RJ, and Zhu X declare non-financial support from Sanofi, during the conduct of the study. The company provided a proportion of the oxaliplatin used in the study for free. The content of the manuscript is solely the responsibility of the authors and does not represent the views of the funder. The funding sources had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of data, preparation, review, or approval of the manuscript nor the decision to submit the manuscript for publication. Wu D, Li XT, and Zhang PJ declare no potential conflicting interests related to this paper.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

safety.

RESULTS

In total, 115 participants (100 males and 15 females; mean age, 57.7 years ± 11.9) were analyzed. The median PFS and OS were 5.0 mo (0.4–58.6 mo) (95% confidence interval (CI): 3.82 to 6.18) *vs* 4.4 mo (1.1–54.4 mo) (95%CI: 2.54 to 6.26; $P = 0.585$) and 8.4 mo (0.4–58.6 mo) (95%CI: 6.88 to 9.92) *vs* 8.3 mo (1.4–54.4 m) (95%CI: 5.71 to 10.96; $P = 0.985$) in the TACE/HAIC + S-1 and TACE/HAIC groups, respectively. The objective response rate and disease control rate were 30.9% *vs* 18.4% and 72.7% *vs* 56.7% in the TACE/HAIC + S-1 and TACE/HAIC groups, respectively. Grade 3/4 adverse events had a similar frequency in both treatment groups.

CONCLUSION

No improvements in tumor response rates, PFS or OS were observed with the addition of S-1 to TACE/HAIC in advanced HCC. Both treatment regimens had a similar safety profile.

Key words: Hepatocellular carcinoma; Advanced; Hepatic arterial infusion chemotherapy; Transarterial chemoembolization; Prognosis; Efficacy

Core tip: This randomized controlled trial showed that the addition of oral S-1 (a composite preparation of a 5-fluorouracil prodrug) to transarterial chemoembolization followed by hepatic arterial infusion chemotherapy with oxaliplatin did not lengthen the survival time of patients with advanced hepatocellular carcinoma complicating portal vein invasion or extrahepatic metastasis, although it did appear to have moderately better anti-tumor activity. Overall, transarterial chemoembolization combined with hepatic arterial infusion chemotherapy was an effective and safe treatment for patients with advanced hepatocellular carcinoma with portal vein invasion or extrahepatic metastasis.

Citation: Guo JH, Liu SX, Gao S, Kou FX, Zhang X, Wu D, Li XT, Chen H, Wang XD, Liu P, Zhang PJ, Xu HF, Cao G, Zhu LZ, Yang RJ, Zhu X. Transarterial chemoembolization with hepatic arterial infusion chemotherapy plus S-1 for hepatocellular carcinoma. *World J Gastroenterol* 2020; 26(27): 3975-3988
URL: https://www.wjgnet.com/1007-9327/full/v26/i27/3975.htm
DOI: https://dx.doi.org/10.3748/wjg.v26.i27.3975

INTRODUCTION

Liver cancer was ranked seventh by number of incident cases and fourth by number of cancer-related deaths worldwide in 2016, with hepatocellular carcinoma (HCC) representing the most prevalent type of liver cancer[1,2]. China currently accounts for approximately 50% of the world's HCC patients, and the high prevalence of chronic hepatitis in this country is thought to be the dominant etiological factor[3,4]. In China, HCC is the second and third most common cause of cancer-related mortality in males and females, respectively[4]. Unfortunately, most patients with HCC are diagnosed at an intermediate or advanced stage at which they are ineligible for potentially curative treatments such as surgical resection and liver transplantation[5,6]. In particular, the prognosis for patients with advanced HCC characterized by vascular tumor invasion and/or extrahepatic metastasis [equal to Barcelona Clinic Liver Cancer (BCLC) stage C or D[7] is almost always very poor[8,9].

Sorafenib, a small molecule inhibitor of vascular endothelial growth factor and platelet-derived growth factor, is widely recommended for the treatment of advanced HCC based on the results of two phase III trials[10,11]. However, several limitations, such as a relatively low response rate, adverse events (AEs) and relatively high cost, are reported to limit the application of sorafenib in clinical practice, especially in Asia[10,12,13]. Transarterial chemoembolization (TACE) has been widely adopted as a treatment for patients with intermediate stage HCC and has also been investigated in

Manuscript source: Unsolicited manuscript

Received: March 29, 2020
Peer-review started: March 29, 2020
First decision: April 25, 2020
Revised: May 7, 2020
Accepted: July 4, 2020
Article in press: July 4, 2020
Published online: July 21, 2020

P-Reviewer: Moriya K
S-Editor: Wang JL
L-Editor: Filipodia
E-Editor: Ma YJ

patients with advanced HCC, including with portal vein invasion, with equivocal results[14,15]. It is hypothesized that the hypoxic injury to tumor cells caused by TACE leads to increased expression of vascular endothelial growth factor, which is a driving factor behind tumor recurrence. Therefore, TACE in combination with sorafenib has been explored. A recent meta-analysis of randomized controlled trials showed that TACE and TACE-sorafenib may improve 1-year survival *versus* sorafenib monotherapy in patients with advanced HCC but did not show a significant difference between these approaches[16]. In addition, the tolerability of sorafenib often leads to dose reductions and interruptions when used in combination with TACE, limiting the effectiveness of this treatment strategy[17-20]. Therefore, further optimization of TACE-based approaches for advanced HCC is required.

Growing evidence suggests that combining TACE with hepatic arterial infusion chemotherapy (HAIC) may provide additional therapeutic benefit for patients with advanced, unresectable HCC[21]. HAIC can significantly increase the local dose of chemotherapeutic agents in the liver and reduce generalized side effects[22,23]. One commonly used chemotherapeutic agent in HAIC procedures is oxaliplatin, which has been shown to be effective and generally well tolerated; previous research indicates that oxaliplatin-based HAIC is tolerable and has potent anti-tumor activity against advanced HCC[24-26]. A study by Gao *et al*[21] showed that combining TACE with HAIC was more effective than TACE alone in patients with intermediate stage HCC. In addition, as access to sorafenib in China is limited for many patients, we also investigated S-1, a composite preparation of a fluorouracil prodrug, which has proven to be a convenient oral chemotherapeutic agent with definite efficacy against advanced unresectable HCC[27,28]. Therefore, we designed this prospective randomized study to evaluate the efficacy and safety of treatment with TACE followed by oxaliplatin-based HAIC, with or without oral S-1, in advanced-stage HCC with portal vein invasion or extrahepatic metastasis.

MATERIALS AND METHODS

Study design and patients

This was a single-center, open-label, prospective, randomized controlled trial conducted between December 2013 and September 2017 with follow-up until November 2018. The study totally included 117 patients aged ≥ 18 years with histologically or clinically diagnosed advanced HCC with portal vein invasion or extrahepatic metastasis (BCLC stage C). Clinical diagnosis of HCC was based on the American Association for the Study of Liver Diseases guideline criteria[29]. Eligible patients were also required to have Child-Pugh class A or B liver function, an Eastern Cooperative Oncology Group performance status of 0 to 1, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, life expectancy ≥ 12 wk, adequate organ function (hemoglobin ≥ 90 g/L, white blood cell count ≥ 3.0×10^9/L, absolute neutrophil count ≥ 1.5×10^9/L, platelet count ≥ 60×10^9/L, serum albumin level > 20 g/L, aspartate transaminase and alanine transaminase < 5 times the upper limit of normal, total bilirubin serum levels < 3 times the upper limit of normal, creatinine clearance rate ≤ 1.5 times the upper limit of normal, and international normalized ratio < 2.3 or partial prothrombin time < 1.5 times the upper limit of normal), and not previously received TACE, HAIC or chemotherapy. Key exclusion criteria were early- or middle-stage HCC, any contraindication to TACE (poor liver function, portal obstruction of at least three segmental branches), advanced cardiac or pulmonary disease and severe renal function impairment, a known medical history of human immunodeficiency virus infection, other invasive malignant diseases and pregnant or breastfeeding women. All recruited patients with hepatitis B virus-related HCC received pre-emptive antiviral therapy.

Written, informed consent was obtained from all participants before entering the study. The clinical trial protocol was approved by the Ethics Committee of our hospital, and the trial was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Randomization and treatments

Participants were randomized 1:1 to receive TACE followed by oxaliplatin-based HAIC plus oral S-1 (TACE/HAIC + S-1) or TACE followed by oxaliplatin-based HAIC (TACE/HAIC). Random assignment was generated by a statistician from our hospital *via* a computer-generated randomization sequence and without stratification.

Treatments were applied every 6 wk until disease progression, death or intolerable toxicity was observed.

TACE

Each patient underwent angiography *via* the femoral artery using Seldinger's technique. Arteriography was routinely performed to collect information about the number, type and location of the tumors and feeding arteries, as well as the presence of vascular anatomic variations. After visualization of the arterial distribution and the portal system in the reflux phase for each individual patient, the most appropriate TACE procedure was selected. The feeding arteries to the lesion were catheterized as selectively as possible by using a highly flexible coaxial catheter (Renegade Hi Flo, Boston Scientific, Boston, MA, United States/Stride ASAHI INTECC, Seto, Japan). The chemoembolization procedure comprised injection of iodized oil (Lipiodol; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France) mixed with 20–40 mg epirubicin hydrochloride (Main Luck Pharmaceutical, Shenzhen, China) as an emulsion into segmental or subsegmental tumor-feeding arteries. For patients with a hepatic arteriovenous fistula, sponge particles (Jinling, Nanjing, China) were used to block the fistula before the infusion of iodized oil.

HAIC

HAIC was performed *via* a catheter. The coaxial catheter was retained in the proper hepatic artery or the left or right hepatic arterial branch following TACE. Oxaliplatin (Eloxatin®; Sanofi S.A., Paris, France) 85 mg/m^2 was continuously infused over 4 hours *via* arterial pumping on day 1. After HAIC was completed, the catheter and sheath were removed. Repeated catheterization was performed in the next treatment cycle.

Oral S-1

S-1 (TS-1®; Taiho Pharmaceutical, Tokyo, Japan) 60 mg was given orally twice daily on days 2–15, initiated from the 2nd d after HAIC, and then patients were allowed to rest for 1 wk. Depending on the TACE and HAIC interval, every 3 wk constituted a course.

Study endpoints and measurements

The primary endpoint was initially designed to be time-to-progression (TTP). However, during the study a large proportion of patients died from liver function failure before tumor progression occurred and not enough progression events were observed for a meaningful estimate of TTP. Therefore, the primary endpoint was changed to progression-free survival (PFS). Progression was defined as progressive disease by an independent radiologic review according to modified RECIST or death from any cause. PFS was defined as the interval between the first TACE treatment and progression or death resulting from any cause.

Secondary endpoints included overall survival (OS), tumor objective response rate (ORR) defined as the proportion of patients achieving a complete (CR) or partial response (PR), disease control rate (DCR) defined as the proportion of patients achieving CR, PR or stable disease (SD) and safety. OS was defined as the interval between the first TACE treatment and death or final follow-up. All tumor response rates were evaluated according to modified RECIST criteria. Adverse reactions were evaluated and graded according to the National Cancer Institute Common Toxicity Criteria (version 4.0). Peripheral neuropathy was graded according to a modified Levi scale.

Physical, clinical, enhanced computed tomography or magnetic resonance imaging and laboratory tests were performed at baseline and at the start of each treatment cycle during the treatment phase. All patients were followed every 2 mo until death or until their final follow-up visit.

Statistical analyses

The study sample size was calculated based on the assumption that the median TTP in patients with advanced HCC receiving TACE followed by HAIC would be 4.0 mo and that adding S-1 would improve the median TTP to 6.5 mo. To detect this difference with 70% power and a 2-sided α of 0.05, 100 participants would be required, with an enrollment period of 24 mo and a follow-up period of 12 mo. Based on an estimated dropout rate of 5%, the target enrollment was set at 110 participants (55 per group).

For all statistical tests, P values < 0.05 were considered significant. Depending on data normality, two-independent-samples t tests or Mann-Whitney U tests were used to assess differences in continuous variables between the groups. The χ^2 test was used to assess between group differences in categorical variables. Tumor response rates

were compared using the two-sided Fisher's exact test. The Kaplan-Meier method was used to calculate estimates of PFS and OS, and data were compared using the log-rank test.

Exploratory univariate and multivariate analyses were conducted to investigate the association between patient demographic and baseline characteristics and survival outcomes (PFS and OS). Any factors that were statistically significant at a P value < 0.10 in the univariate analysis were candidates for entry into the multivariate model. All statistical analyses were performed using SPSS software (version 22; IBM SPSS Statistics, Armonk, NY, United States). The statistical methods of this study were reviewed by Xiao-Ting Li from our hospital.

RESULTS

Study participants

Between December 2013 and September 2017, 230 patients were screened, and 117 were randomly assigned to TACE/HAIC + S-1 (n = 56) or TACE/HAIC (n = 61) (Figure 1). Two participants withdrew consent before receiving treatment (one patient in each treatment group) and were therefore excluded from final analysis. Baseline characteristics were comparable between the two treatment groups (Table 1). Overall, participants were predominantly male and infected with HBV, and all participants had portal vein invasion or extrahepatic metastasis; 76/115 (66.1%) patients had portal vein invasion, 79/115 (68.7%) patients had extrahepatic metastasis and 40/115 (34.8%) patients had both portal vein invasion and extrahepatic metastasis. Extrahepatic metastasis sites included retroperitoneal lymph nodes (50 patients), lungs (18 patients), adrenal glands (10 patients), bones (8 patients) and other sites (6 patients). Ten patients had at least two sites of extrahepatic metastases.

Treatment exposure

The total number of cycles of treatment received was 150 and 163 for patients in the TACE/HAIC + S-1 and TACE/HAIC groups, respectively. Patients in both groups received a median of two cycles (1−9cycles) of TACE and HAIC. Curative surgical resection was conducted for 1/55 (1.8%) patient in the TACE/HAIC + S-1 group and 2/60 (3.3%) patients in the TACE/HAIC group following downstaging. TACE combined with local ablation was conducted for 8/55 (14.5%) patients in the TACE/HAIC + S-1 group and 9/60 (15.0%) patients in the TACE/HAIC group. TACE combined with radioactive particle implantation was conducted for 1/60 (1.7%) patient in the TACE/HAIC group.

Tumor response

Numerically higher ORR and DCR were observed for patients receiving TACE/HAIC + S-1 than those receiving TACE/HAIC (30.9% *vs* 18.4%, P = 0.176 and 72.7% *vs* 56.7%, P = 0.109, respectively). Rates of CR, PR, SD and progressive disease in the TACE/HAIC + S-1 group were 7.3%, 23.6%, 41.8%, 27.3%, respectively, and in the TACE/HAIC group were 6.7%, 11.7%, 38.3%, 43.3%, respectively (Table 2).

Survival

After a median follow-up period of 8.3 mo (0.4–58.6 mo), the median PFS for patients receiving TACE/HAIC + S-1 and TACE/HAIC was similar: 5.0 mo (0.4−58.6 mo; 95% confidence interval (CI): 3.82 to 6.18) and 4.4 mo (1.1−54.4 mo; 95%CI: 2.50 to 6.30) (P = 0.585) (Figure 2A). The median OS was also similar between the two groups: 8.4 mo (0.4−58.6 mo; 95%CI: 7.03 to 9.76) and 8.3 mo (1.4−54.4 mo; 95%CI: 6.00 to 10.60) (P = 0.985), respectively (Figure 2B). The PFS rates at 3, 6, 9 and 12 mo were 67.3%, 41.8%, 23.6% and 19.7%, respectively, in the TACE/HAIC + S-1 group and 65.0%, 41.7%, 18.7% and 11.2%, respectively, in the TACE/HAIC group. The OS rates at 3, 6, 9 and 12 mo were 85.5%, 63.6%, 41.8% and 32.5%, respectively, in the TACE/HAIC + S-1 group and 83.1%, 64.5%, 45.3% and 36.6%, respectively, in the TACE/HAIC group.

Follow-up

By the last follow-up, 20 patients were alive (9 patients in the TACE/HAIC + S-1 group and 11 patients in the TACE/HAIC group). In the TACE/HAIC + S-1 group, 3 patients received other treatments after progression, 3 patients were lost to follow-up, and 3 patients achieved a CR. In the TACE/HAIC group, 3 patients received sorafenib, 2 received other treatments after progression, 2 patients were lost to follow-up, 3

Table 1 Summary of patient demographics and baseline disease characteristics, *n* (%)

Variable	TACE/HAIC + S-1, *n* = 55	TACE/HAIC, *n* = 60	*P* value
Age in yr			0.210
mean ± SD (range)	56.3 ± 10.9 (34-81)	59.1 ± 12.7 (22-82)	
Sex			0.709
Male	49 (89.1)	51 (85.0)	
Female	6 (10.9)	9 (15.0)	
Liver disease etiology			0.237
HBV	47 (85.5)	45 (75.0)	
HCV	4 (7.3)	6 (10.0)	
HBV and HCV	1 (1.8)	0	
Unknown	3 (5.5)	9 (15.0)	
Performance status			0.756
0	40 (72.7)	41 (68.3)	
1	15 (27.3)	19 (31.7)	
Child-Pugh stage			0.642
A	47 (85.5)	55 (91.7)	
B	8 (14.5)	5 (8.3)	
Tumor maximal size in cm			0.530
mean ± SD (range)	9.7 ± 4.7 (2.2-25.3)	10.2 ± 4.2 (2.5-21.0)	
Number of tumors			0.683
1	16 (29.1)	19 (31.7)	
≥ 2	34 (61.8)	38 (63.3)	
Infiltrative	5 (9.1)	3 (5.0)	
Portal vein invasion			0.649
No invasion	21 (38.2)	18 (30.0)	
Stage I-II	24 (43.6)	30 (50.0)	
Stage III-IV	10 (18.2)	12 (20.0)	
Extrahepatic metastasis			0.274
Yes	41 (74.5)	38 (63.3)	
No	14 (25.5)	22 (36.7)	
Targeted treatment			0.846
Yes	9 (16.4)	8 (13.3)	
No	46 (83.6)	52 (86.7)	
AFP in ng/mL			0.579
Median (range)	4833 (0.9-1974770)	5561 (0.6-1207090)	

AFP: Alpha-fetoprotein; HAIC: Hepatic arterial infusion chemotherapy; SD: Standard deviation; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TACE: Transarterial chemoembolization.

patients achieved a CR and 1 patient achieved a PR.

Association between patient baseline factors and survival

Univariable and multivariable Cox regression analyses (Table 3 and Table 4) showed that the number of tumors and gamma-glutamyl transferase were predictive factors for PFS, and the number of tumors, gamma-glutamyl transferase and the tumor

Table 2 Response rates according to modified Response Evaluation Criteria in Solid Tumors criteria, *n* (%)

Response	Treatment group			*P* value
	Overall cohort	TACE/HAIC + S-1, *n* = 55	TACE/HAIC, *n* = 60	
CR	8	4 (7.3)	4 (6.7)	1.000
PR	20	13 (23.6)	7 (11.7)	0.148
SD	46	23 (41.8)	23 (38.3)	0.849
PD	41	15 (27.3)	26 (43.3)	0.109
ORR	28	17 (30.9)	11 (18.3)	0.176
DCR	74	40 (72.7)	34 (56.7)	0.109

CR: Complete response; DCR: Disease control rate; HAIC: Hepatic arterial infusion chemotherapy; ORR: Objective response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease; TACE: Transarterial chemoembolization.

response were predictive factors for OS. However, age, sex, tumor size, portal vein invasion, extrahepatic metastasis, S-1 treatment and target treatment showed no significance as predictive factors.

Safety

In both treatment groups the most common AEs were transient liver injury (including elevation of serum liver enzymes and bilirubin), vomiting, abdominal nonspecific pain and fever (Table 5). Abdominal pain occurred frequently during HAIC and 2–3 d after TACE. This pain was adequately controlled by temporarily stopping the infusion of oxaliplatin or by the application of analgesics. Hematologic AEs observed included leukopenia, thrombocytopenia and anemia, and rates of theses AEs were also similar between the two treatment groups. One patient in the TACE/HAIC group experienced cerebral lipiodol embolism, however, they recovered after symptomatic treatment. The main AE related to S-1 was tolerable nausea. No incidences of neuropathy were observed in either group and no treatment-related death was observed.

DISCUSSION

The use of TACE combined with HAIC or systemic chemotherapy in patients with BCLC stage C HCC remains a controversial therapeutic approach. To the authors' knowledge, the present study represents the first randomized, controlled trial of sequential TACE and HAIC plus oral S-1 in advanced HCC. Although the study did not meet its revised primary endpoint of PFS, a higher ORR and DCR were observed with the addition of S-1 to TACE/HAIC; 30.9% *vs* 18.4% and 72.7% *vs* 56.7%, respectively. The inability of the current study to detect a difference in survival may have been due to the poor prognosis of the patient population, who all had portal vein invasion or extrahepatic metastasis as mandated in the inclusion criteria. Additionally, our study suggests that both TACE/HAIC + S-1 and TACE/HAIC have acceptable safety profiles and are generally well tolerated by patients with advanced HCC.

In our study, treatment with TACE/HAIC + S-1 or TACE/HAIC led to an ORR of 30.9% and 18.4% and DCR of 72.7% and 56.7% and a median PFS of 5.0 and 4.4 mo, respectively. Compared with the findings of the present study, a previous phase II non-randomized controlled study showed higher rates of ORR (68.9%) and a longer median PFS (8.0 mo) for TACE/HAIC in patients with advanced HCC, although it should be mentioned that this study excluded patients with portal vein invasion or extrahepatic metastasis[21]. The large difference in response rates and PFS observed between our study and this previous study almost certainly reflects that the patient population in our study included those with portal vein invasion and/or extrahepatic metastasis, for whom prognosis is usually extremely poor[15,30]. Additionally, the median OS in the present study was 8.4 mo and 8.3 mo for patients receiving TACE/HAIC + S-1 and TACE/HAIC, respectively. These results are broadly comparable if not slightly higher than the median OS reported from a combined sub-analysis of the two Phase III trials of sorafenib in patients with advanced HCC with macrovascular invasion (n = 162; 184 d, approximately 6.1 mo) and extrahepatic

Table 3 Univariable and multivariable Cox regression analyses for progression-free survival

Factor	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age in yr	0.99 (0.97-1.01)	0.215	-	-
Sex as female/male	0.73 (0.42-1.29)	0.283	-	-
Tumor size in cm	1.04 (1.00-1.09)	0.040[1]	1.04 (0.99-1.08)	0.098
Number of tumors				
1	-	0.004[1]	-	0.028[1]
≥ 2	0.28 (0.12-0.62)	0.002[1]	0.36 (0.15-0.85)	0.019[1]
Infiltrative	0.48 (0.23-1.01)	0.052	0.60 (0.28-1.30)	0.193
Portal vein invasion				
No invasion	-	0.566	-	-
Stage I-II	0.75 (0.43-1.30)	0.303	-	-
Stage III-IV	0.89 (0.54-1.47)	0.645	-	-
Extrahepatic metastasis	1.25 (0.83-1.89)	0.285	-	-
Child-Pugh stage, A/B	1.13 (0.62-2.06)	0.702	-	-
Performance status, 0/1	1.10 (0.73-1.66)	0.651	-	-
AFP in ng/mL	1.00 (1.00-1.00)	0.050	1.00 (1.00-1.00)	0.212
Albumin in g/L	0.97 (0.93-1.02)	0.246	-	-
Total bilirubin in mg/mL	1.02 (1.00-1.04)	0.088	1.00 (1.00-1.02)	0.960
GGT	1.00 (1.00-1.00)	0.003[1]	1.00 (1.00-1.00)	0.032[1]
ALT	1.00 (1.00-1.01)	0.114	-	-
AST	1.00 (1.00-1.01)	0.008[1]	1.00 (1.00-1.01)	0.149
Targeted treatment, yes/no	0.86 (0.50-1.49)	0.589	-	-
S-1 treatment, yes/no	0.90 (0.61-1.32)	0.585	-	-

[1]The *P* value is < 0.05. CI: Confidence interval; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; HR: Hazard ratio.

metastasis (n = 261; 223 d, approximately 7.4 mo)[30].

Patients with BCLC Stage C HCC, with portal vein invasion or extrahepatic metastasis, were selected for this study because most other studies of HAIC have focused on patients with moderate-stage HCC and Child-Pugh class A liver function. At the time our study was initiated, sorafenib was the only recommended treatment for advanced HCC in most international guidelines. However, the ORR associated with sorafenib in advanced HCC with portal vein invasion or extrahepatic metastasis is relatively low (2%−3.3%)[10,11]. Sorafenib is also not easily accessible for many patients in China due to the relatively high cost of treatment. In addition, TACE alone also has limited efficacy in HCC with portal vein invasion[31,32]. Although liver cancer cells are relatively resistant to chemotherapeutic drugs, HAIC can provide significantly higher drug concentration ratios locally in tumor tissue compared with peripheral tissue and can promote a permanent antitumor immune response. The relatively higher survival observed in this study *vs* previous results with sorafenib in similar patient sub-populations may reflect that HAIC combined with TACE is more effective than HAIC or TACE alone. There are several factors supporting this hypothesis. Firstly, tumor cell hypoxia induced by TACE can enhance the antitumor effects of oxaliplatin. Secondly, the continuous hepatic arterial infusion of oxaliplatin can kill residual cancer cells after TACE, especially those that remain active. Finally, S-1 provides the possibility of improving extrahepatic tumor control.

In addition to systemic therapies and HAIC, localized irradiation is also an alternative treatment for patients with advanced HCC characterized by vascular invasions. Selective internal radiotherapy with yttrium-90, or radioembolization,

Table 4 Univariable and multivariable Cox regression analyses for overall survival

Factor	Univariable analysis		Multivariable analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age in yr	1.00 (0.98-1.02)	0.911	-	-
Sex as female/male	0.83 (0.45-1.53)	0.559	-	-
Tumor size in cm	1.01 (0.96-1.05)	0.722	-	-
Number of tumors				
1	-	< 0.001[1]	-	0.012[2]
≥ 2	0.18 (0.08-0.41)	< 0.001[1]	0.27 (0.11-0.68)	0.005[2]
Infiltrative	0.33 (0.15-0.71)	0.004[2]	0.47 (0.21-1.05)	0.067
Portal vein invasion				
No invasion	-	0.648	-	-
Stage I-II	0.83 (0.46-1.50)	0.533	-	-
Stage III-IV	1.02 (0.58-1.78)	0.946	-	-
Extrahepatic metastasis	1.37 (0.88-2.14)	0.168	-	-
Child-Pugh stage, A/B	1.39 (0.74-2.62)	0.305	-	-
Performance status, 0/1	1.14 (0.74-1.76)	0.560	-	-
AFP in ng/mL	1.00 (1.00-1.00)	0.016[2]	1.00 (1.00-1.00)	0.192
Albumin in g/L	0.97 (0.92-1.02)	0.188	-	-
Total bilirubin in mg/mL	1.03 (1.00-1.05)	0.019[2]	1.01 (0.98-1.03)	0.505
GGT	1.00 (1.00-1.00)	< 0.001[1]	1.00 (1.00-1.00)	0.060
ALT	1.00 (1.00-1.01)	0.625	-	-
AST	1.00 (1.00-1.01)	0.127	-	-
Target treatment, yes/no	0.65 (0.35-1.19)	0.163	-	-
S-1 treatment, yes/no	1.00 (0.67-1.50)	0.985	-	-
Tumor response				
CR	-	< 0.001[1]	-	< 0.001[1]
PR	0.02 (0.00-0.07)	< 0.001[1]	0.02 (0.00-0.09)	< 0.001[1]
SD	0.11 (0.06-0.21)	< 0.001[1]	0.11 (0.06-0.22)	< 0.001[1]
PD	0.20 (0.12-0.32)	< 0.001[1]	0.20 (0.12-0.32)	< 0.001[1]

[1]The *P* value is < 0.001.

[2]The *P* value is < 0.05. CI: Confidence interval; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CR: Complete response; GGT: Gamma-glutamyl transferase; HR: Hazard ratio; PD: Progressive disease; PR: Partial response; SD: Stable disease.

which is one of the intra-arterial treatments, can also be performed in patients with intermediate to advanced HCC[33]. However, selective internal radiotherapy is higher cost and unavailable in China. With the technical development of radiotherapy, stereotactic body radiation therapy can deliver high precision and intensity radiation to tumor tissue while sparing surrounding tissue. In a systematic review and meta-analysis including 2577 patients with unresectable HCC, subgroup analyses showed nonsignificant survival benefit in the TACE plus radiotherapy group compared with the TACE alone group for patients with portal vein tumor thrombosis[34]. In summary, further studies are necessary to evaluate localized irradiation value in the treatment of advanced HCC.

The major limitation of this study was that the primary endpoint had to be adjusted from TTP to PFS due to the high number of patients experiencing death from liver failure before disease progression. However, because TTP and PFS are closely related endpoints, we consider that the sample size calculation and study power would have

Table 5 Observed adverse events according to common terminology criteria for adverse events grading, *n* (%)

Adverse event	TACE/HAIC + S-1, *n* = 55	TACE/HAIC, *n* = 60	*P* value
Liver injury			0.243
Grades 1-2	28 (50.9)	23 (38.3)	
Grades 3-4	27 (49.1)	37 (61.7)	
Vomiting			0.478
Grades 1-2	23 (41.8)	29 (48.3)	
Grades 3-4	1 (1.8)	0 (0)	
Abdominal pain			0.820
Grades 1-2	37 (67.3)	37 (61.7)	
Grades 3-4	10 (18.2)	13 (21.7)	
Fever			0.277
Grades 1-2	45 (81.8)	44 (73.3)	
Grades 3-4	0 (0)	0 (0)	
Leukopenia			0.465
Grades 1	2 (3.6)	4 (6.7)	
Grades 2-4	0 (0)	0 (0)	
Thrombocytopenia			0.793
Grade 1	9 (16.4)	11 (18.3)	
Grade 2	7 (12.7)	7 (11.7)	
Grade 3	0 (0)	1 (1.7)	
Grade 4	0 (0)	0 (0)	
Anemia			0.220
Grade 1	7 (12.7)	15 (25.0)	
Grade 2	2 (3.6)	5 (8.3)	
Grade 3	1 (1.8)	1 (1.7)	
Grade 4	0 (0)	0 (0)	

HAIC: Hepatic arterial infusion chemotherapy; TACE: Transarterial chemoembolization.

only been marginally affected by this change in endpoint. Another limitation of this study was its open-label nature, which meant that subsequent treatments for patients who stopped study treatment may have been influenced by the investigator and patient decisions.

In conclusion, the addition of S-1 to sequential TACE and oxaliplatin-based HAIC did not lead to improved PFS or OS in patients with advanced HCC with portal vein invasion and/or extrahepatic metastasis, although anti-tumor effect appeared to be greater with the addition of S-1. Both treatment regimens were similarly well tolerated by patients. Given that systemic therapy has only limited benefit for this patient population and is inaccessible for patients in many countries, and based on the promising results achieved with TACE and HAIC, identifying a strategy to derive the optimal benefit from these approaches remains an unmet need.

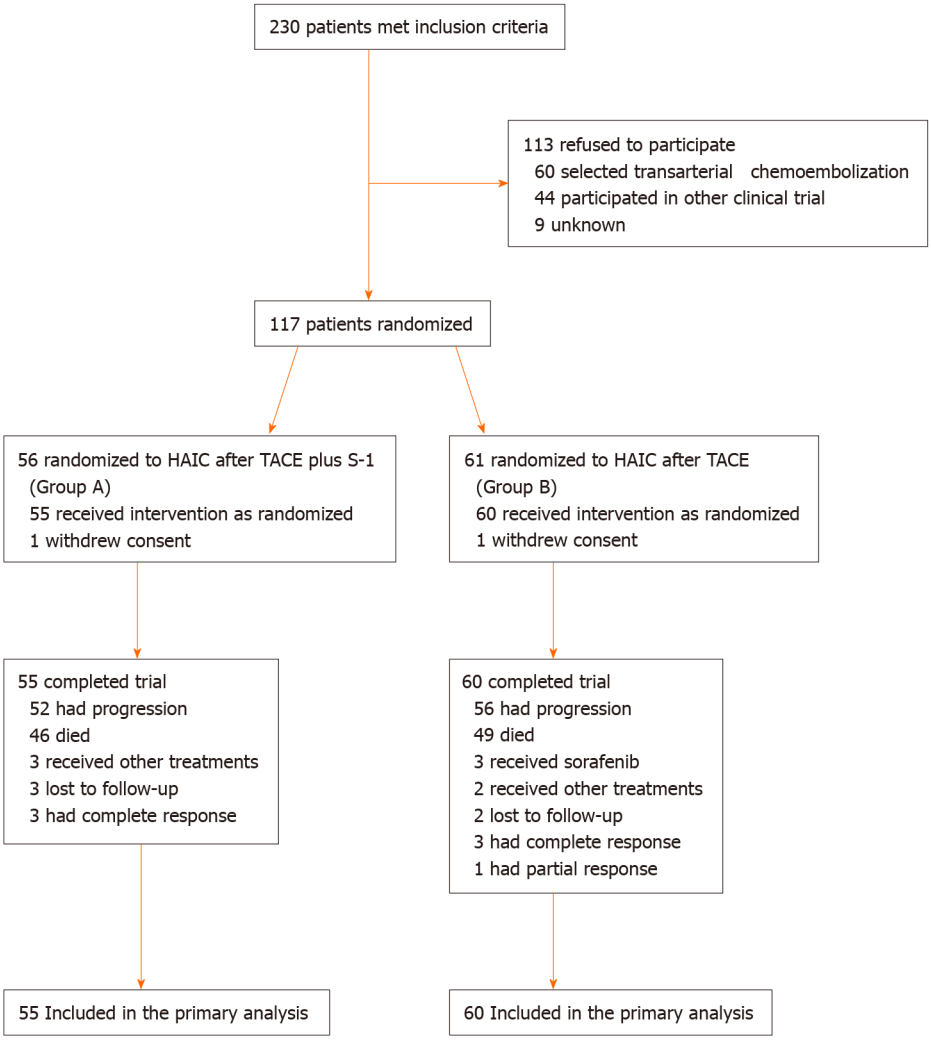

Figure 1 CONSORT flow diagram. TACE: Transarterial chemoembolization; HAIC: Hepatic arterial infusion chemotherapy.

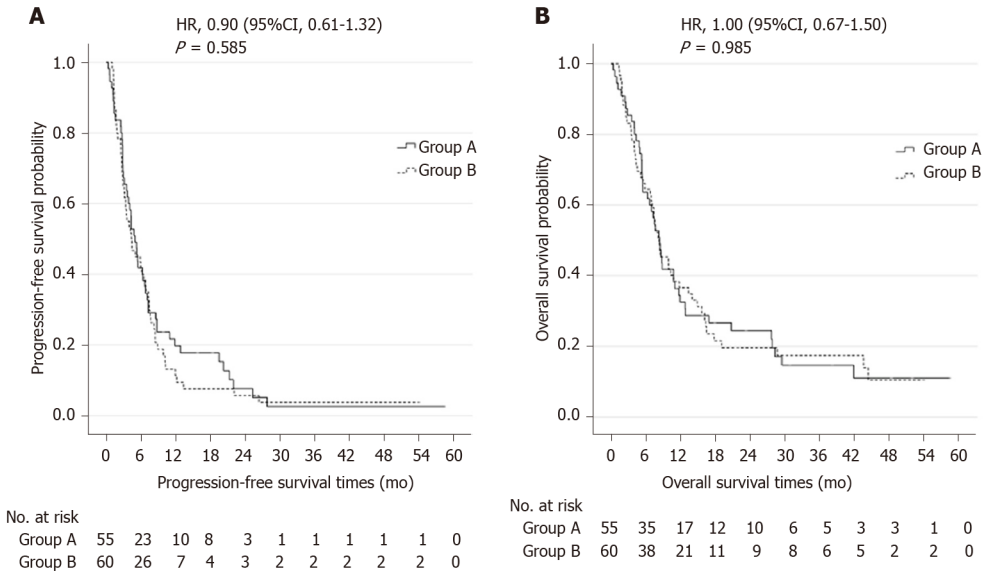

Figure 2 Kaplan-Meier curves. A: Curves of progression-free survival; B: Curves of overall survival. Group A indicates hepatic arterial infusion chemotherapy after transarterial chemoembolization plus S-1. Group B indicates hepatic arterial infusion chemotherapy after transarterial chemoembolization. HR: Hazard ratio.

ARTICLE HIGHLIGHTS

Research background

The prognosis for patients with advanced hepatocellular carcinoma (HCC) characterized by vascular tumor invasion and/or extrahepatic metastasis is almost always very poor. Systemic therapy with sorafenib was the only recommended first-line therapy for these patients at the beginning of this study. Transarterial chemoembolization (TACE) is recommended for the treatment of patients with intermediate stage HCC, although it has been investigated in patients with more advanced disease with equivocal results. Hepatic arterial infusion chemotherapy (HAIC) has shown promising local benefits for advanced HCC. S-1 has proven to be a convenient oral chemotherapeutic agent with definite efficacy against advanced HCC.

Research motivation

Sorafenib had shown limited benefit and was not easily accessible for many patients due to high cost. Other therapeutic approaches such as TACE and HAIC have been investigated in clinical practice, particularly in the Asia Pacific region. However, equivocal data mean that these approaches remain controversial in patients with advanced HCC. Novel treatment strategies are therefore being sought, and TACE followed by HAIC with oxaliplatin has shown promising preliminary results.

Research objectives

To evaluate the efficacy and safety of treatment with TACE followed by oxaliplatin-based HAIC, with or without oral S-1, in advanced-stage HCC with portal vein invasion and/or extrahepatic metastasis, we use progression-free survival (PFS) as the primary endpoint and overall survival (OS), objective response rate, disease control rate and safety as the secondary endpoints.

Research methods

In this single-center, open-label, randomized, controlled trial, patients with advanced HCC were randomized (1:1) to receive TACE (epirubicin 20-40 mg) followed by oxaliplatin-based HAIC (oxaliplatin 85 mg/m^2) either with (TACE/HAIC + S-1) or without (TACE/HAIC) oral S-1 60 mg twice daily.

Research results

Our results showed that the addition of oral S-1 to TACE followed by HAIC with oxaliplatin did not lengthen PFS and OS, although numerically higher objective response rate and disease control rate were observed for TACE/HAIC with S-1 *vs* without S-1 (30.9% *vs* 18.4% and 72.7% *vs* 56.7%). Both treatment regimens were similarly well tolerated by patients.

Research conclusions

In conclusion, TACE combined with HAIC was an effective and safe treatment for patients with advanced HCC with portal vein invasion and/or extrahepatic metastasis, although the addition of S-1 to sequential TACE and oxaliplatin-based HAIC did not lead to improved PFS or OS.

Research perspectives

Given that systemic therapy has only limited benefit and is inaccessible for patients with advanced HCC in many countries, and based on the promising results achieved with TACE and HAIC, identifying a strategy to derive the optimal benefit from these approaches remains an unmet need.

REFERENCES

1 **European Association For The Study Of The Liver**. European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

2 **Global Burden of Disease Cancer Collaboration**, Fitzmaurice C, Akinyemiju TF, Al Lami FH, Alam T, Alizadeh-Navaei R, Allen C, Alsharif U, Alvis-Guzman N, Amini E, Anderson BO, Aremu O, Artaman A, Asgedom SW, Assadi R, Atey TM, Avila-Burgos L, Awasthi A, Ba Saleem HO, Barac A, Bennett JR, Bensenor IM, Bhakta N, Brenner H, Cahuana-Hurtado L, Castañeda-Orjuela CA, Catalá-López F, Choi JJ, Christopher DJ, Chung SC, Curado MP, Dandona L, Dandona R, das Neves J, Dey S, Dharmaratne SD, Doku DT, Driscoll TR, Dubey M, Ebrahimi H, Edessa D, El-Khatib Z, Endries AY, Fischer F, Force LM,

Foreman KJ, Gebrehiwot SW, Gopalani SV, Grosso G, Gupta R, Gyawali B, Hamadeh RR, Hamidi S, Harvey J, Hassen HY, Hay RJ, Hay SI, Heibati B, Hiluf MK, Horita N, Hosgood HD, Ilesanmi OS, Innos K, Islami F, Jakovljevic MB, Johnson SC, Jonas JB, Kasaeian A, Kassa TD, Khader YS, Khan EA, Khan G, Khang YH, Khosravi MH, Khubchandani J, Kopec JA, Kumar GA, Kutz M, Lad DP, Lafranconi A, Lan Q, Legesse Y, Leigh J, Linn S, Lunevicius R, Majeed A, Malekzadeh R, Malta DC, Mantovani LG, McMahon BJ, Meier T, Melaku YA, Melku M, Memiah P, Mendoza W, Meretoja TJ, Mezgebe HB, Miller TR, Mohammed S, Mokdad AH, Moosazadeh M, Moraga P, Mousavi SM, Nangia V, Nguyen CT, Nong VM, Ogbo FA, Olagunju AT, Pa M, Park EK, Patel T, Pereira DM, Pishgar F, Postma MJ, Pourmalek F, Qorbani M, Rafay A, Rawaf S, Rawaf DL, Roshandel G, Safiri S, Salimzadeh H, Sanabria JR, Santric Milicevic MM, Sartorius B, Satpathy M, Sepanlou SG, Shackelford KA, Shaikh MA, Sharif-Alhoseini M, She J, Shin MJ, Shiue I, Shrime MG, Sinke AH, Sisay M, Sligar A, Sufiyan MB, Sykes BL, Tabarés-Seisdedos R, Tessema GA, Topor-Madry R, Tran TT, Tran BX, Ukwaja KN, Vlassov VV, Vollset SE, Weiderpass E, Williams HC, Yimer NB, Yonemoto N, Younis MZ, Murray CJL, Naghavi M. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2018; **4**: 1553-1568 [PMID: 29860482 DOI: 10.1001/jamaoncol.2018.2706]

3 **Tanaka M**, Katayama F, Kato H, Tanaka H, Wang J, Qiao YL, Inoue M. Hepatitis B and C virus infection and hepatocellular carcinoma in China: a review of epidemiology and control measures. *J Epidemiol* 2011; **21**: 401-416 [PMID: 22041528 DOI: 10.2188/jea.je20100190]

4 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

5 **Llovet JM**. Updated treatment approach to hepatocellular carcinoma. *J Gastroenterol* 2005; **40**: 225-235 [PMID: 15830281 DOI: 10.1007/s00535-005-1566-3]

6 **Shah SA**, Smith JK, Li Y, Ng SC, Carroll JE, Tseng JF. Underutilization of therapy for hepatocellular carcinoma in the medicare population. *Cancer* 2011; **117**: 1019-1026 [PMID: 20945363 DOI: 10.1002/cncr.25683]

7 **Forner A**, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis* 2010; **30**: 61-74 [PMID: 20175034 DOI: 10.1055/s-0030-1247133]

8 **Chan SL**, Chong CC, Chan AW, Poon DM, Chok KS. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. *World J Gastroenterol* 2016; **22**: 7289-7300 [PMID: 27621575 DOI: 10.3748/wjg.v22.i32.7289]

9 **Minagawa M**, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. *World J Gastroenterol* 2006; **12**: 7561-7567 [PMID: 17171782 DOI: 10.3748/wjg.v12.i47.7561]

10 **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]

11 **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]

12 **Jackson R**, Psarelli EE, Berhane S, Khan H, Johnson P. Impact of Viral Status on Survival in Patients Receiving Sorafenib for Advanced Hepatocellular Cancer: A Meta-Analysis of Randomized Phase III Trials. *J Clin Oncol* 2017; **35**: 622-628 [PMID: 28045619 DOI: 10.1200/JCO.2016.69.5197]

13 **Park JW**, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35**: 2155-2166 [PMID: 25752327 DOI: 10.1111/liv.12818]

14 **Omata M**, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int* 2017; **11**: 317-370 [PMID: 28620797 DOI: 10.1007/s12072-017-9799-9]

15 **Chern MC**, Chuang VP, Liang CT, Lin ZH, Kuo TM. Transcatheter arterial chemoembolization for advanced hepatocellular carcinoma with portal vein invasion: safety, efficacy, and prognostic factors. *J Vasc Interv Radiol* 2014; **25**: 32-40 [PMID: 24290099 DOI: 10.1016/j.jvir.2013.10.013]

16 **Chen QF**, Wu PH, Huang T, Shen LJ, Huang ZL, Li W. Efficacy of treatment regimens for advanced hepatocellular carcinoma: A network meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2019; **98**: e17460 [PMID: 31577775 DOI: 10.1097/MD.0000000000017460]

17 **Cammà C**, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, Andreone P, Craxì A, Cottone M. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. *Radiology* 2002; **224**: 47-54 [PMID: 12091661 DOI: 10.1148/radiol.2241011262]

18 **Chung GE**, Lee JH, Kim HY, Hwang SY, Kim JS, Chung JW, Yoon JH, Lee HS, Kim YJ. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. *Radiology* 2011; **258**: 627-634 [PMID: 21273524 DOI: 10.1148/radiol.10101058]

19 **Luo J**, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, Shi M. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. *Ann Surg Oncol* 2011; **18**: 413-420 [PMID: 20839057 DOI: 10.1245/s10434-010-1321-8]

20 **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 versus 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]

21 **Gao S**, Zhang PJ, Guo JH, Chen H, Xu HF, Liu P, Yang RJ, Zhu X. Chemoembolization alone vs combined chemoembolization and hepatic arterial infusion chemotherapy in inoperable hepatocellular carcinoma patients. *World J Gastroenterol* 2015; **21**: 10443-10452 [PMID: 26420971 DOI: 10.3748/wjg.v21.i36.10443]

22 **Ikeda M**, Shimizu S, Sato T, Morimoto M, Kojima Y, Inaba Y, Hagihara A, Kudo M, Nakamori S, Kaneko S, Sugimoto R, Tahara T, Ohmura T, Yasui K, Sato K, Ishii H, Furuse J, Okusaka T. Sorafenib plus hepatic arterial infusion chemotherapy with cisplatin versus sorafenib for advanced hepatocellular carcinoma: randomized phase II trial. *Ann Oncol* 2016; **27**: 2090-2096 [PMID: 27573564 DOI: 10.1093/annonc/mdw323]

23 **Obi S**, Sato S, Kawai T. Current Status of Hepatic Arterial Infusion Chemotherapy. *Liver Cancer* 2015; **4**: 188-199 [PMID: 26674592 DOI: 10.1159/000367746]

24 **He M**, Li Q, Zou R, Shen J, Fang W, Tan G, Zhou Y, Wu X, Xu L, Wei W, Le Y, Zhou Z, Zhao M, Guo Y, Guo R, Chen M, Shi M. Sorafenib Plus Hepatic Arterial Infusion of Oxaliplatin, Fluorouracil, and Leucovorin vs Sorafenib Alone for Hepatocellular Carcinoma With Portal Vein Invasion: A Randomized Clinical Trial. *JAMA Oncol* 2019; **5**: 953-960 [PMID: 31070690 DOI: 10.1001/jamaoncol.2019.0250]

25 **Rathore R**, Safran H, Soares G, Dubel G, McNulty B, Ahn S, Iannitti D, Kennedy T. Phase I study of hepatic arterial infusion of oxaliplatin in advanced hepatocellular cancer: a brown university oncology group study. *Am J Clin Oncol* 2010; **33**: 43-46 [PMID: 19687731 DOI: 10.1097/COC.0b013e31819d8668]

26 **Yen Y**, Lim DW, Chung V, Morgan RJ, Leong LA, Shibata SI, Wagman LD, Marx H, Chu PG, Longmate JA, Lenz HJ, Ramanathan RK, Belani CP, Gandara DR. Phase II study of oxaliplatin in patients with unresectable, metastatic, or recurrent hepatocellular cancer: a California Cancer Consortium Trial. *Am J Clin Oncol* 2008; **31**: 317-322 [PMID: 18845988 DOI: 10.1097/COC.0b013e318162f57d]

27 **Furuse J**, Okusaka T, Kaneko S, Kudo M, Nakachi K, Ueno H, Yamashita T, Ueshima K. Phase I/II study of the pharmacokinetics, safety and efficacy of S-1 in patients with advanced hepatocellular carcinoma. *Cancer Sci* 2010; **101**: 2606-2611 [PMID: 20946314 DOI: 10.1111/j.1349-7006.2010.01730.x]

28 **Nagata H**, Hatano E, Asechi H, Narita M, Yanagida A, Yasuchika K, Ikai I, Uemoto S. [Retrospective analysis of clinical results in eight patients with advanced hepatocellular carcinoma with lung metastases treated by TS-1]. *Gan To Kagaku Ryoho* 2007; **34**: 233-235 [PMID: 17301534]

29 **Heimbach JK**, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, Zhu AX, Murad MH, Marrero JA. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018; **67**: 358-380 [PMID: 28130846 DOI: 10.1002/hep.29086]

30 **Bruix J**, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. *J Hepatol* 2017; **67**: 999-1008 [PMID: 28687477 DOI: 10.1016/j.jhep.2017.06.026]

31 **Kim GA**, Shim JH, Yoon SM, Jung J, Kim JH, Ryu MH, Ryoo BY, Kang YK, Lee D, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS. Comparison of chemoembolization with and without radiation therapy and sorafenib for advanced hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. *J Vasc Interv Radiol* 2015; **26**: 320-9.e6 [PMID: 25612807 DOI: 10.1016/j.jvir.2014.10.019]

32 **Koo JE**, Kim JH, Lim YS, Park SJ, Won HJ, Sung KB, Suh DJ. Combination of transarterial chemoembolization and three-dimensional conformal radiotherapy for hepatocellular carcinoma with inferior vena cava tumor thrombus. *Int J Radiat Oncol Biol Phys* 2010; **78**: 180-187 [PMID: 19926229 DOI: 10.1016/j.ijrobp.2009.07.1730]

33 **Mazzaferro V**, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchianò A, Bongini M, Lanocita R, Civelli E, Bombardieri E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013; **57**: 1826-1837 [PMID: 22911442 DOI: 10.1002/hep.26014]

34 **Huo YR**, Eslick GD. Transcatheter Arterial Chemoembolization Plus Radiotherapy Compared With Chemoembolization Alone for Hepatocellular Carcinoma: A Systematic Review and Meta-analysis. *JAMA Oncol* 2015; **1**: 756-765 [PMID: 26182200 DOI: 10.1001/jamaoncol.2015.2189]

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