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 conduct, 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 conduct 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.

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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
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

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Core tip: This randomized controlled trial showed that the addition of oral S-1 (a composite preparation of a 5-fluourouracil 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 antitumor 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.

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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[1-3]. 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[4,5]. In China, HCC is the second and third most common cause of cancer-related mortality in males and females, respectively[6]. 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[7]. 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] is almost always very poor[8-10].

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[8,11,12]. 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[12,13]. Transarterial chemoembolization (TACE) has been widely adopted as a treatment for patients with intermediate stage HCC and has also been investigated in...
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**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. 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/m² 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 \( \chi^2 \) 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 extrhepatic metastasis; 76/115 (66.1%) patients had portal vein invasion, 79/115 (68.7%) patients had extrhepatic metastasis and 40/115 (34.8%) patients had both portal vein invasion and extrhepatic metastasis. Extrhepatic 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 extrhepatic 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 (1−9 cycles) 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%, 32.5% and 32.5%, 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 mean ± SD (range)     | 56.3 ± 10.9 (34-81)      | 59.1 ± 12.7 (22-82) | 0.210   |
| 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                    | 4833 (0.9-1974770)       | 5561 (0.6-120790) | 0.579   |

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 | Overall cohort | TACE/HAIC + S-1, n = 55 | TACE/HAIC, n = 60 | P value |
|----------|----------------|--------------------------|-------------------|---------|
| 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.

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 these 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 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.
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)    | 0.0401                | 1.04 (0.99-1.08)    | 0.098                |
| Number of tumors              |                     |                       |                     |                      |
| 1                             | -                   | 0.0041                | -                   | 0.0281               |
| ≥ 2                           | 0.28 (0.12-0.62)    | 0.0021                | 0.36 (0.15-0.85)    | 0.0191               |
| 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)    | 0.0031                | 1.00 (1.00-1.00)    | 0.0321               |
| ALT                           | 1.00 (1.00-1.01)    | 0.114                 | -                   | -                    |
| AST                           | 1.00 (1.00-1.01)    | 0.0081                | 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                 | -                   | -                    |

1The 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)The 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%)The relatively higher survival observed in this study vs previous results with sorafenib in similar patient subpopulations 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<sup>1</sup>    | -                | 0.01<sup>2</sup> |
| ≥ 2                         | 0.18 (0.08-0.41)     | < 0.001<sup>1</sup>    | 0.27 (0.11-0.68) | 0.005<sup>3</sup> |
| Infiltrative                | 0.33 (0.15-0.71)     | 0.004<sup>2</sup>      | 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<sup>2</sup>      | 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<sup>2</sup>      | 1.01 (0.98-1.03) | 0.505   |
| GGT                         | 1.00 (1.00-1.00)     | < 0.001<sup>1</sup>    | 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<sup>1</sup>    | -                | < 0.001<sup>1</sup> |
| PR                          | 0.02 (0.00-0.07)     | < 0.001<sup>1</sup>    | 0.02 (0.00-0.09) | < 0.001<sup>1</sup> |
| SD                          | 0.11 (0.06-0.21)     | < 0.001<sup>1</sup>    | 0.11 (0.06-0.22) | < 0.001<sup>1</sup> |
| PD                          | 0.20 (0.12-0.32)     | < 0.001<sup>1</sup>    | 0.20 (0.12-0.32) | < 0.001<sup>1</sup> |

<sup>1</sup>The P value is < 0.001.
<sup>2</sup>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<sup>33</sup>. 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<sup>34</sup>. 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.
230 patients met inclusion criteria
113 refused to participate
60 selected transarterial chemoembolization
44 participated in other clinical trial
9 unknown
117 patients randomized

56 randomized to HAIC after TACE plus S-1
(Group A)
55 received intervention as randomized
1 withdrew consent

61 randomized to HAIC after TACE
(Group B)
60 received intervention as randomized
1 withdrew consent

55 completed trial
52 had progression
46 died
3 received other treatments
3 lost to follow-up
3 had complete response

60 completed trial
56 had progression
49 died
3 received sorafenib
2 received other treatments
2 lost to follow-up
3 had complete response
1 had partial response

55 included in the primary analysis
60 included in the primary analysis

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/m²) 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.

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