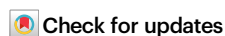


Apatinib plus hepatic arterial infusion of oxaliplatin and raltitrexed for hepatocellular carcinoma with extrahepatic metastasis: phase II trial

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Most patients with advanced hepatocellular carcinoma (HCC) ultimately experience tumor progression after first-line systemic therapies. Systemic therapy is generally recommended as second-line treatment for advanced HCC in the major guidelines. Combining apatinib with hepatic arterial infusion chemotherapy (HAIC) likely drives synergistic activity on advanced HCC with extrahepatic metastasis. This phase II trial (ChiCTR2000029082) aimed to assess efficacy and safety of this combination in patients with HCC with extrahepatic metastasis who have progressed after first-line systemic therapies. The primary end point was the objective response rate (ORR). The secondary endpoints were progress-free survival (PFS), disease control rate (DCR), 6- and 12-month survival rates, overall survival (OS), and adverse events (AEs). Thirty-nine patients received oral treatment with apatinib, and hepatic artery infusion oxaliplatin plus raltitrexed. Per RECIST v1.1, the ORR and DCR was 53.8% and 89.7% in the patients population, respectively. The median PFS and OS was 6.2 months and 11.3 months, respectively. The 6- and 12-month survival rates were 81.7% and 44.1%, respectively. All AEs were manageable by medication or dose modifications. Apatinib plus HAIC for second-line therapy in advanced HCC with extrahepatic metastasis shows promising efficacy and manageable toxicities.

According to Barcelona Clinical Liver Cancer (BCLC) staging system, hepatocellular carcinoma (HCC) with extrahepatic metastasis is classified as advanced stage (BCLC stage C) along with portal vein invasion¹. Extrahepatic metastases are depicted by imaging at the time of initial diagnosis in 13–37% of patients with HCC^{2,3}. Although there are different treatment methods for HCC in different stages

worldwide, systemic therapies are usually the recommended treatment options in the major HCC guidelines for HCC with extrahepatic metastasis^{4–7}.

Systemic therapy for advanced HCC has made great progress since sorafenib, and many systemic therapies have been successfully used as second-line treatments for advanced HCC, such as tyrosine

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kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs)^{8–11}. However, compared to systemic therapy alone, the combination of systemic therapy and loco-regional therapy may have a better efficacy for advanced HCC, especially for advanced HCC who have progression of intrahepatic lesions after systematic therapy¹².

Apatinib is a small-molecule TKI, which blocks tumor angiogenesis and inhibits tumor growth by targeting VEGFR-2¹³. In a series of trials^{14–16}, apatinib has shown encouraging antitumor efficacy and acceptable toxicities in some malignant tumor. In a randomized, placebo-controlled, phase III trial (AHELP study)¹⁷, apatinib monotherapy, as a second-line or later treatment, was administered to patients with advanced HCC. The objective response rate (ORR) was 11% (95% CI, 7–15), and the median progress-free survival (PFS) and overall survival (OS) were 4.5 months (95% CI, 3.9–4.7) and 8.7 months (95% CI, 7.5–9.8), respectively. Moreover, apatinib was recommended as a second-line treatment for patients with advanced HCC by the Chinese HCC guideline¹⁸.

Hepatic arterial infusion chemotherapy (HAIC) can directly provide sustained high concentrations of chemotherapy drugs to liver tumors, which is related to local anti-tumor effects. The efficacy of HAIC in the application of advanced HCC with lesions limited to the liver has been clarified, and recently the combination therapy of HAIC and TKI has shown satisfactory antitumor outcomes^{19,20}. Moreover, a retrospective study has shown that HAIC, as a loco-regional treatment method, also showed a certain efficacy in HCC with extrahepatic metastasis²¹.

The anti-tumor mechanism of raltitrexed is to selectively inhibit thymidylate synthase, and synthesize polyglutamic acid compounds through folate based polyglutamic acid synthase in cells. Its inhibitory effect on thymidylate synthase is strong, and it stays in cells for a long time²². Compared to the extremely short plasma concentration half-life of fluorouracil (only 5–20 min)²³, the plasma concentration of raltitrexed showed a three-phase decrease after administration, with a final half-life of 8.2 to 105 h²⁴. Raltitrexed can be administered for HCC patients in a shorter period of time (1 h), while fluorouracil requires a longer period of continuous administration (usually ≥ 46 h)^{19,25}. This is an advantage of raltitrexed, which may improve the patient's tolerance and adherence. Like HAIC with cisplatin, 5-fluorouracil (5-FU), cisplatin plus 5-FU, or oxaliplatin plus 5-FU, HAIC with oxaliplatin plus raltitrexed was also an efficacious and safe treatment for patients with advanced HCC^{26,27}.

Here we report a phase II, prospective clinical trial of apatinib and HAIC with oxaliplatin plus raltitrexed in patients with HCC with extrahepatic metastasis who had progressed in intrahepatic lesions after first-line systemic therapy. The study showed that combining apatinib with HAIC resulted in encouraging efficacy in patients with HCC with extrahepatic metastasis.

Results

Patient population

From April 2021 and September 2022, a total 47 patients were screened. Among them, 39 patients (31 males and 8 females; median age, 55 years; range, 28–73 years) were enrolled in the patient population (Fig. 1). The distant metastasis sites were lung, adrenal gland, bone, and abdominal cavity. Among the sites of extrahepatic metastasis, lung and lymph nodes were the most common sites, with 25 patients (64.1%) of lung metastasis and 16 patients (41.0%) of lymph node metastasis. There were 13 patients (33.3%) with multiple systemic metastases and 26 patients (66.7%) with single metastasis (Table 1).

By the data cutoff date of January 31, 2023, the median follow-up period was 20.0 months (95% CI: 16.5–23.5). Out of 39 patients, 32 (82.1%) had discontinued the trial, while 7 (17.9%) patients were still receiving the study treatment, including one patient who was still receiving apatinib plus HAIC and six patients who were still receiving apatinib monotherapy (Fig. 1).

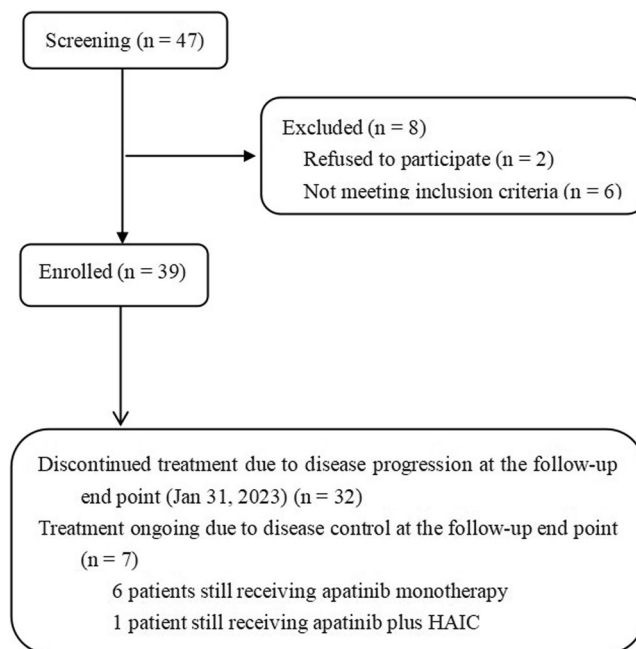


Fig. 1 | Study profile. HAIC hepatic arterial infusion chemotherapy.

Efficacy

The primary outcome of the study was ORR according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). In the first stage of the studies Simon's two-stage design, nine of the 19 patients who could be evaluated in the first stage of this study showed an objective response (47.4%), meeting the threshold to continue the study into the second stage.

After the second stage, objective response was achieved in 21 (53.8%) of the 39 patients in the patient population. 21 patients achieved partial response, 14 patients achieved stable disease, and 4 patients achieved progressive disease. Disease control was achieved in 35 (89.7%) of 39 patients in the patient population (Table 2).

Based on modified RECIST (mRECIST), objective response was achieved in 24 (61.5%) of the 39 patients in the patient population. 21 patients achieved partial responses, 11 patients achieved stable disease, and 4 achieved progressive disease. Disease control was achieved in 35 (89.7%) of the 39 patients (Table 2; Figs. 2 and 3).

Target intrahepatic and extrahepatic lesions shrinkage were noted in 34 (87.2%) and 29 (74.4%) of 39 patients after treatment, and the mean best percentage change of the target intrahepatic and extrahepatic lesions size from the baseline were −24.2% (SD 0.28) and −18.8% (SD 0.37) (Figs. 4 and 5).

The median PFS was 6.2 months (95% CI, 4.8–7.6) (Fig. 6). The median intrahepatic control period and extrahepatic control period were 7.0 (95% CI, 4.8–9.2) months and 6.2 (95% CI, 5.0–7.4) months, respectively. There was no significant difference in the median intrahepatic control period and extrahepatic control period ($P = 0.383$) (Fig. 7).

The 6- and 12-month survival rates were 81.7% (SD, 5.9%) and 44.1% (SD, 8.1%), respectively. The median OS was 11.3 months (95% CI, 8.5–14.1) (Fig. 8).

Safety

We analyzed the safety data in all 39 patients only presenting treatment-related adverse events (AEs). A treatment-related AE included any adverse event that in the investigator's opinion may have been caused by the study drugs or HAIC procedure with reasonable possibility. There was no report of death. Grade 4 AEs included thrombocytopenia 1 patient (2.6%) and elevated aspartate aminotransferase 1

Table 1 | Baseline characteristics of the patient population (n = 39)

Characteristic	Patients, n (%)
Gender	
Male	31 (79.4%)
Female	8 (20.5%)
Age (years), median (range)	52 (28–73)
Eastern Cooperative Oncology Group score	
0	15 (38.5%)
1	21 (53.8%)
2	3 (7.7%)
Maximum tumour size, cm	
≤10	23 (59.0%)
>10	16 (41.0%)
Number of HCC foci	
≤3	4 (10.3%)
>3	35 (91.3%)
Child-Pugh class	
A (5 points)	18 (46.2%)
A (6 points)	14 (35.9%)
B (7 points)	7 (17.9%)
Liver cirrhosis	
No	15 (38.5%)
Yes	24 (61.5%)
Serum α-fetoprotein concentration, ng/ml	
>400	28 (71.8%)
≤400	11 (28.2%)
Portal vein invasion grade	
None	11 (28.2%)
Vp1–2	10 (25.6%)
Vp3	13 (33.3%)
Vp4	5 (12.8%)
Sites of extrahepatic lesions	
Lungs	25 (64.1%)
Lymph Nodes	16 (41.0%)
Regional	14 (35.9%)
Distant	2 (5.1%)
Adrenal	2 (5.1%)
Bone	1 (2.6%)
Abdominal cavity	1 (2.6%)
Extent of extrahepatic metastasis	
Multiple metastasis	13 (33.3%)
Single metastasis*	26 (66.7%)
Etiologic factor	
HBV (with or without HCV)	33 (84.6%)
HCV (with or without HBV)	3 (7.7%)
Other (without HBV or HCV)	3 (7.7%)
Subsequent systemic therapy	
Sorafenib	1
Regorafenib	5
Lenvatinib	2
PD-1 antibody	15

HBV hepatitis B virus, HCV hepatitis C virus, HCC hepatocellular carcinoma, Vp1 third branch portal vein invasion, Vp2 second branch portal vein invasion, Vp3 first branch portal vein invasion, Vp4 main portal vein invasion. *Only lymph node metastasis is defined as single metastasis.

patient (2.6%). Grade 3 AEs were leukopenia (2 [5.1%]), thrombocytopenia (3 [7.7%]), alanine aminotransferase increased (2 [5.1%]), aspartate aminotransferase increased (3 [7.7%]), hypertension (10 [25.6%]), hand-foot syndrome (5 [12.8%]), proteinuria (3 [7.7%]), and sepsis (1 [2.6%]) (Table 3). Two cases of infectious diseases, including cholecystitis and sepsis, occurred in the combination stage of apatinib plus HAIC and were resolved within 2 weeks of antibiotic treatment.

Thirty (77%) of 39 patients had apatinib dose modifications, of whom 16 (53%) patients only needed to reduce the dose once, and 14 (47%) patients needed to reduce the dose twice. Seventeen (57%) of 30 patients reduced the dose of apatinib during or at the end of treatment in the first cycle, and the first dose reduction of apatinib was recorded in three (10%) patients in the second cycle, five (17%) patients in the third cycle, two (7%) patient in the fourth cycle, two (7%) patient in the fifth cycle, and one (3%) patient in the sixth cycle. Twelve (31%) of 39 patients had dose modifications of two chemotherapeutic drugs, of whom 5 (42%) patients reduced the dose once and 7 (58%) patients reduced the dose twice. Among the 7 patients with two chemotherapeutic drugs dose reductions, three (43%) patients terminated HAIC prematurely after achieving a partial response and were considered by the researchers to be benefiting from treatment and remained in the trial.

At the follow-up end point, 39 patients received a total of 150 cycles of HAIC (mean, 3.8; SD, 1.7). Nine (23.1%) patients completed six cycles of HAIC. The median exposure times of apatinib were 7.2 months, ranging from 1.0 to 22.0 months.

Discussion

In Asian countries, the staging and treatment of advanced HCC with and without extrahepatic metastasis (portal vein invasion) are usually differentiated, and loco-regional therapies including HAIC were performed as treatment option for advanced HCC with portal invasion following the management guidelines of HCC^{5,6,28}. However, in most of trials, the two types of advanced HCC had not been distinguished, or extrahepatic metastasis was merely mentioned in the stratified analysis of advanced HCC. Both systemic and loco-regional therapies are suitable for advanced HCC with portal vein invasion, but loco-regional therapy for advanced HCC with extrahepatic metastasis is undoubtedly not the best choice. This phase II study is to evaluate the combination of a VEGFR TKI and HAIC for advanced HCC with extrahepatic metastasis.

Nowadays, systemic therapy, which was recommended second-line treatment for advanced HCC in the major guidelines, mainly focuses on TKIs and ICIs, including combination therapy or monotherapy^{8–11,29–32}. In the several trials of ICI alone or with TKI as second-line therapies for advanced HCC, the ORR of the combination of nivolumab (PD-1 inhibitor) and ipilimumab (cytotoxic T-lymphocyte associated protein 4) was the highest, reaching 32%^{32,33}. However, the curative benefits for patients with advanced HCC remained unsatisfactory. The ORR in this study was significantly higher, and although this was not a head-to-head comparative study, the outcomes in this study were still worth looking forward to.

Compared with the AHELP study of apatinib monotherapy for advanced HCC as a second-line treatment¹⁷, apatinib plus HAIC had a better ORR, a longer PFS, and a higher 6-month survival rate in this study. In this study, the proportion of patients with intrahepatic lesions shrinkage was higher than that with extrahepatic lesions (87.2% vs. 74.4%), moreover, the median intrahepatic control period was longer than the median extrahepatic control period (7.0 months vs. 6.2 months). Therefore, there was potential synergistic effects between HAIC and apatinib for advanced HCC. Although these were not head-to-head comparative studies, the results still indicated that HAIC treatment for intrahepatic lesions potentially accelerated the reduction of the burden of intrahepatic lesions, which might lead to better tolerance of patients to apatinib, prolonging the exposure time of apatinib (7.2 months vs. 3.6 months), and might help improve the

Table 2 | Tumor response in patient population (n = 39) (according to RECIST v1.1 and mRECIST)

Evaluation criteria	Best tumor response				ORR (%) 95% CI	DCR (%) 95% CI
	CR	PR	SD	PD		
RECIST v1.1	0	21	14	4	21/39 (53.8%) (37.5–70.2)	35/39 (89.7%) (79.8–99.7)
mRECIST	3	21	11	4	24/39 (61.5%) (45.6–77.5)	35/39 (89.7%) (79.8–99.7)

RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1, mRECIST modified Response Evaluation Criteria in Solid Tumors, CR complete response, PR partial response, SD stable disease, PD progressive disease, ORR objective response rate, DCR disease control rate.

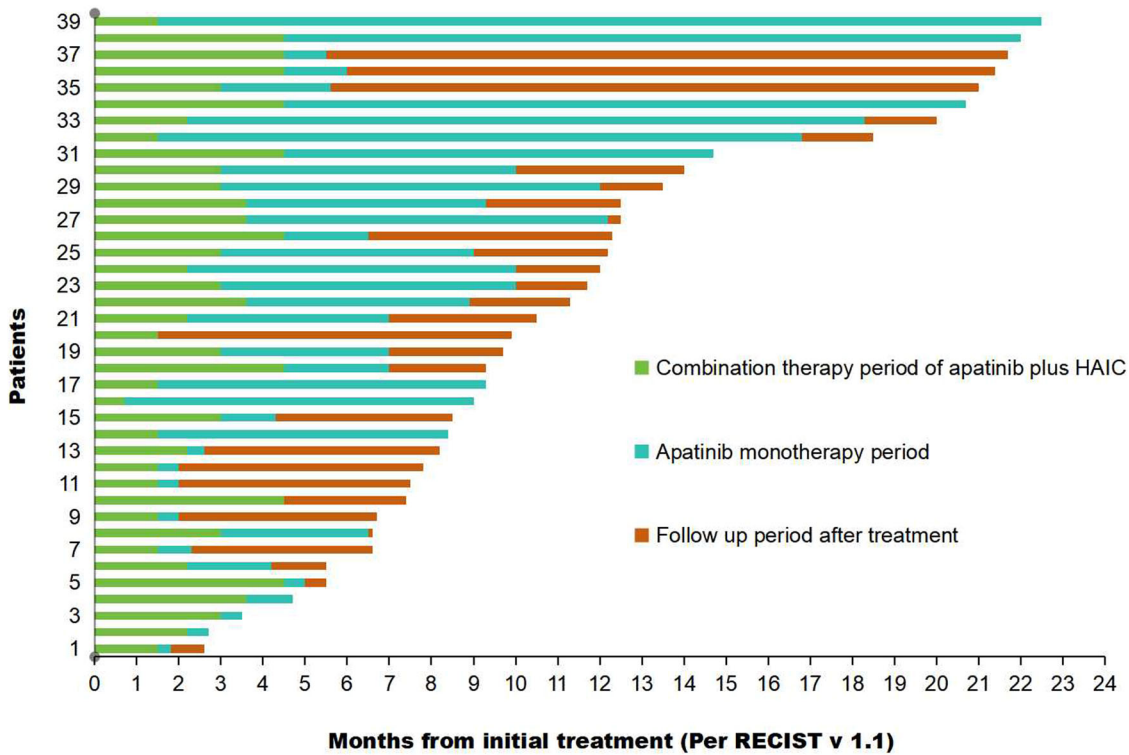


Fig. 2 | Treatment protocol exposure and response duration per RECIST v1.1. HAIC hepatic arterial infusion chemotherapy; RECIST v1.1 Response Evaluation Criteria in Solid Tumors version 1.1.

antitumor effect of apatinib. Furthermore, more patients had the opportunity to receive subsequent antitumor treatments, due to the better tumor control by apatinib, thus obtaining better survival benefits. The addition of HAIC treatment to anti-angiogenic treatment has been shown to improve the outcomes of advanced HCC. In previous studies^{19,20}, the combination therapy of HAIC and sorafenib showed better antitumor outcomes than sorafenib alone. Additionally, a previous retrospective study³⁴ showed that for patients with advanced HCC, the efficacy of apatinib combined with transcatheter arterial chemoembolization (TACE) was superior to that of TACE alone, indicating that the combination of apatinib with loco-regional therapy of liver could effectively improve the clinical efficacy for advanced HCC. In this study, lung and lymph nodes were the most common sites of extrahepatic metastasis of advanced HCC. This finding was consistent with that of Sanjeev K et al. who analyzed the location of extrahepatic metastasis in 403 patients with advanced HCC². In the TRIPLET phase II trial³⁵, HAIC combined with apatinib and PD-1 inhibitors were used to treat advanced HCC patients as a first-line treatment. The triple therapy had better ORR (77.1%) and disease control rate (97.1%), as well as longer PFS (10.38 months), and 17.1% of patients achieved tumor downstaging and received curative therapy. There was no patient who underwent curative therapy due to tumor downstaging after treatment in this study. Combined immunotherapy

might further enhance the efficacy of HAIC plus apatinib in the treatment of advanced HCC patients, and further comparative studies were needed to demonstrate its effectiveness. The safety profile of our trial was composed of AEs related to apatinib and HAIC. Hypertension, hand-foot syndrome, oral ulcer and proteinuria were considered to be related to apatinib as an anti-angiogenic TKI agent, and most cases of AEs were grade 1 to 3 in this trial, which were generally consistent with previous studies in HCC with orally administered apatinib^{17,36}. AEs attributable to HAIC with oxaliplatin plus raltitrexed have been reported in a previous study²⁶. In this trial, the incidences of 29.5% for abdominal pain were observed, and two cases (4.5%) of infectious diseases occurred after treatment, one case of sepsis and one case of cholecystitis, which were considered to be related to HAIC. Occurrence of other AEs, including gastrointestinal toxicity, hematological toxicity and liver dysfunction, might be associated with the combination treatment. Compared with the AHELP study of apatinib monotherapy, the incidence of liver injury was low, with hyperbilirubinemia and elevated levels of ALT and AST in this study. In the SILIUS study³⁷, HAIC combined with sorafenib also showed slightly lower liver injury compared to sorafenib alone (including elevated ALT, AST, and total bilirubin). Furthermore, HAIC plus sorafenib significantly reduced the incidence of hyperbilirubinemia compared to sorafenib alone in the FOHAIC-1 study (any

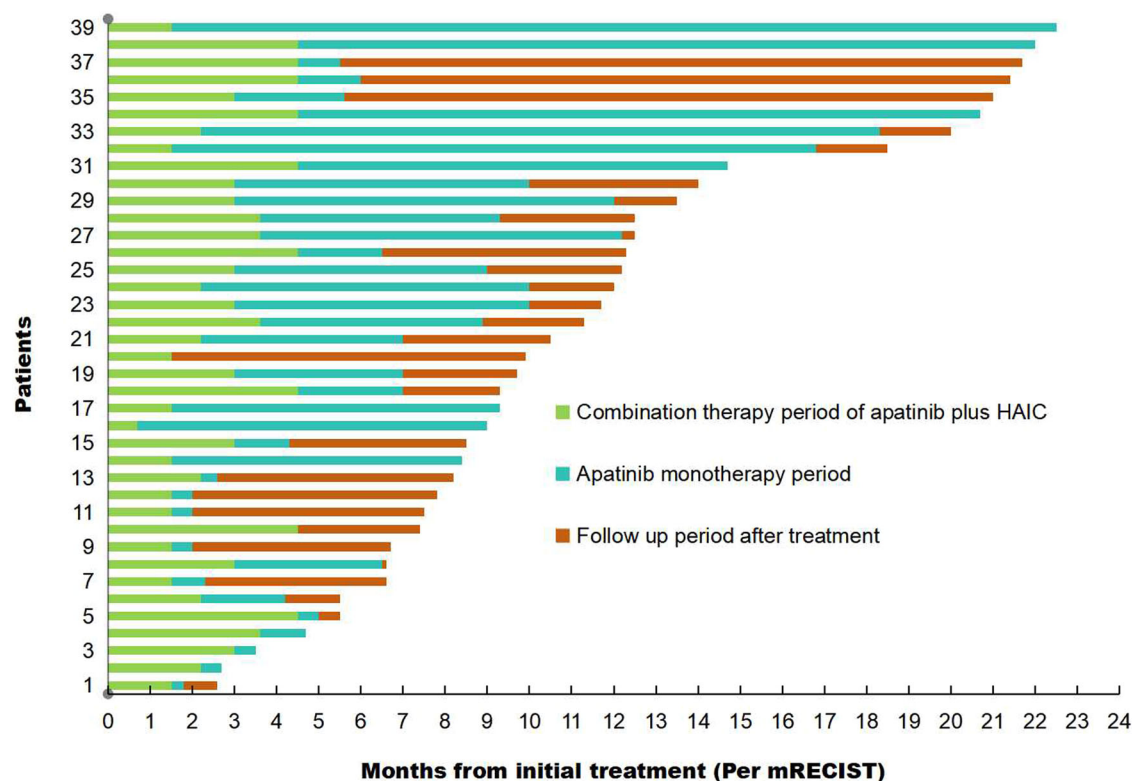


Fig. 3 | Treatment protocol exposure and response duration per mRECIST. HAIC hepatic arterial infusion chemotherapy; mRECIST modified Response Evaluation Criteria in Solid Tumors.

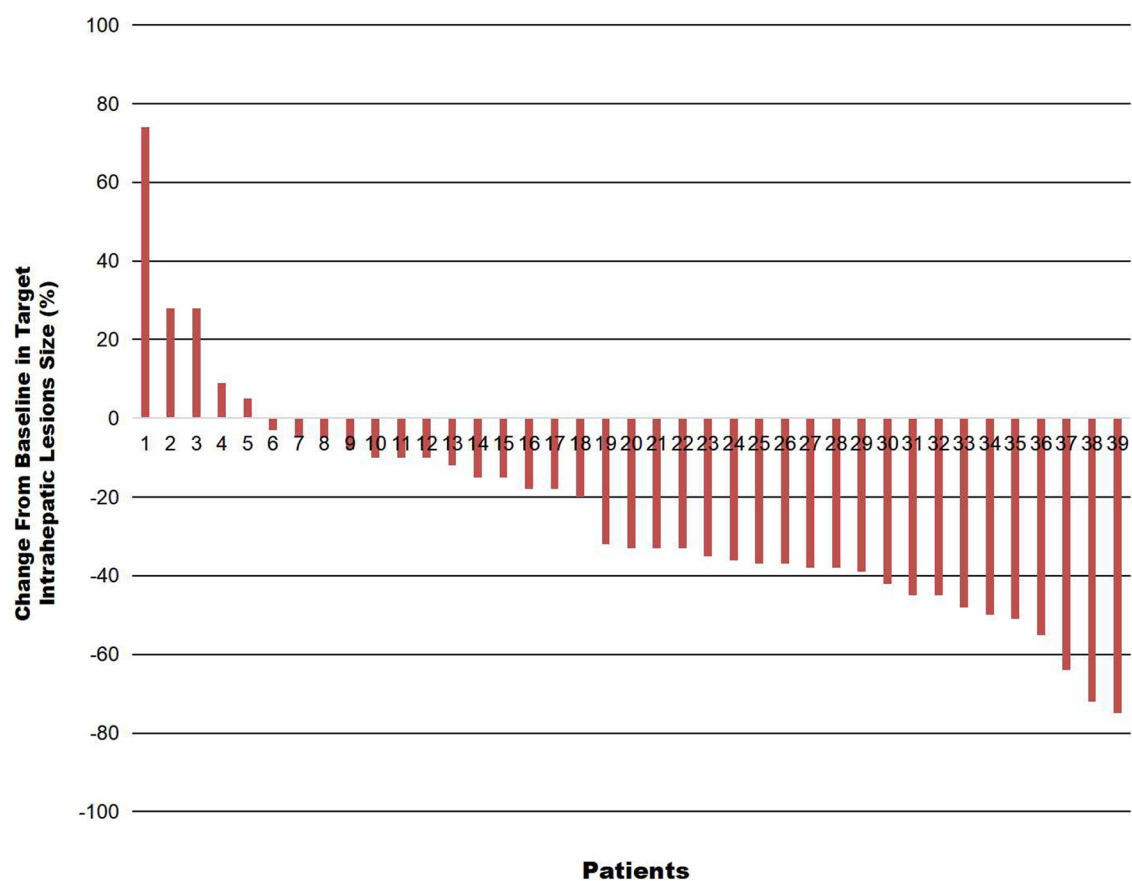


Fig. 4 | Waterfall plot for the best percentage change in target intrahepatic lesions size. Shown are the best percentage change in target intrahepatic lesions size after treatment in 39 patients who underwent apatinib plus hepatic arterial infusion chemotherapy.

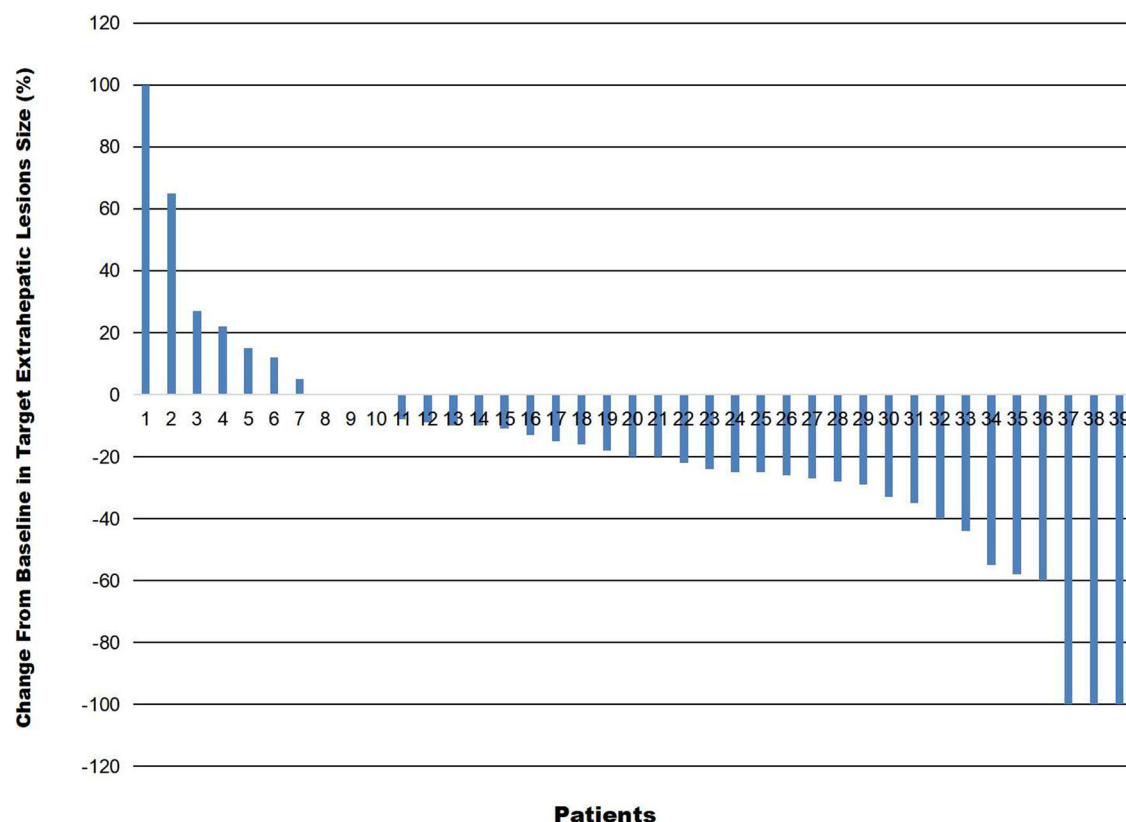


Fig. 5 | Waterfall plot for the best percentage change in target extrahepatic lesions size. Shown are the best percentage change in target extrahepatic lesions size after treatment in 39 patients who underwent apatinib plus hepatic arterial infusion chemotherapy. Three patients had 0% change from baseline.

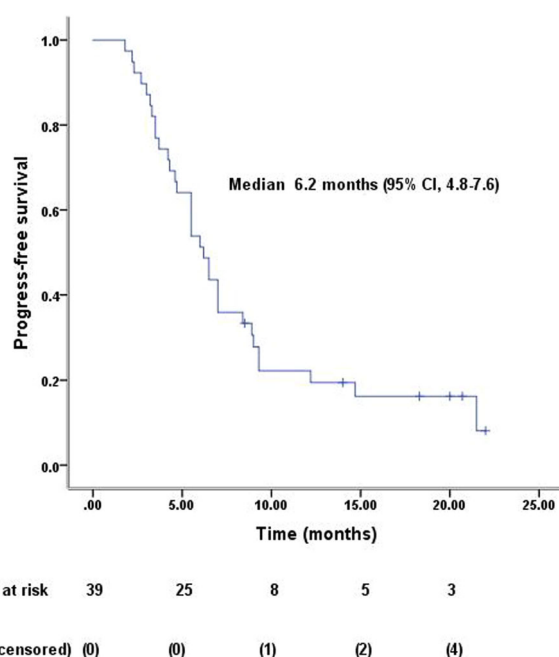


Fig. 6 | Progression-free survival. Shown are Kaplan-Meier curves for progression-free survival in 39 patients. The median progression-free survival was 6.2 months (95% CI, 4.8–7.6).

grade: 17.2% vs 35.7%)³⁸. This might be related to the rapid reduction of intrahepatic lesion burden by HAIC, which enables patients to have better tolerance to apatinib. All AEs were manageable by medication or dose reduction.

This study has several limitations. Firstly, due to the lack of a control arm in our single-arm design, it is difficult to attribute the observed benefits solely to the addition of HAIC to apatinib. Secondly, the proportion of participants with dose modifications of the study agents, especially apatinib, was higher than expected. However, almost all participants continued to receive study treatment after medication or dose modifications.

In conclusion, apatinib plus HAIC has promising efficacy and manageable toxicities in this trial, making it a promising option for second-line treatment in patients with advanced HCC with extrahepatic metastases. Multicenter phase III randomized controlled trials are warranted to further demonstrate these findings.

Methods

Study design and participants

This was a multicenter, open-label, single-arm, phase II trial done at 5 hospitals in China, with Simon's two-stage optimal design. The trial was approved by the Ethics Committee of Fujian Cancer Hospital (Fuzhou, China) (K2020-016-02). The study design and conduct complied with all relevant regulations regarding the use of human study participants and was conducted in accordance with the criteria set by the Declaration of Helsinki. All patients involved in the trial provided written informed consent. This study was registered with www.chictr.org.cn, number ChiCTR2000029082.

The first patient was enrolled on 1 April 2019 and the last patient on 26 September 2022. Eligible HCC patients were diagnosed based on histological examination, contrast-enhanced CT, or MRI findings⁷. Patients aged 18–75 years who had progressed to a first-line systemic therapy (defined as the radiological progression of intrahepatic lesions during the initial first-line systemic therapy or within 6 months after a first-line systemic therapy) with advanced HCC with extrahepatic metastasis were eligible to participate the study. Extrahepatic

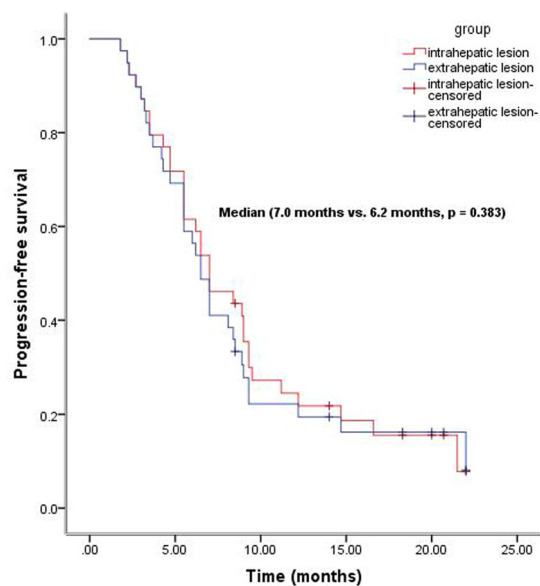


Fig. 7 | Intrahepatic control period and extrahepatic control period. Shown are Kaplan–Meier curves for intrahepatic control period and extrahepatic control period in 39 patients. The median intrahepatic control period and extrahepatic control period were 7.0 (95% CI, 4.8–9.2) months and 6.2 (95% CI, 5.0–7.4) months, respectively ($P = 0.383$).

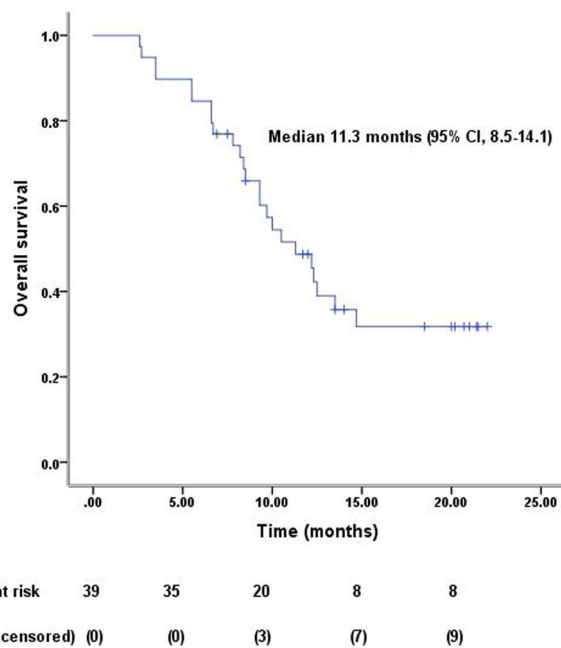


Fig. 8 | Overall survival. Shown are Kaplan–Meier curves for time to overall survival in 39 patients. The median overall survival was 11.3 months (95% CI, 8.5–14.1).

metastasis included distant metastasis or lymph node metastasis. Other inclusion criteria were: (1) Eastern Cooperative Oncology Group performance score of 0–2, (2) Child-Pugh class of A or B (7 points), (3) adequate hematologic values (leukocyte count $>3000/\text{mm}^3$, absolute

Table 3 | Treatment-related adverse events of the patient population ($n = 39$) (according to CTCAE v4.03)

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
Leucopenia	8 (20.5%)	5 (12.8%)	2 (5.1%)	0
Anemia	2 (5.1%)	1 (2.6%)	0	0
Thrombocytopenia	2 (5.1%)	4 (10.3%)	3 (7.7%)	1 (2.6%)
Hyperbilirubinemia	2 (5.1%)	1 (2.6%)	0	0
Alanine aminotransferase increased	6 (15.4%)	2 (5.1%)	2 (5.1%)	0
Aspartate aminotransferase increased	7 (17.9%)	3 (7.7%)	3 (7.7%)	1 (2.6%)
Fever	10 (25.6%)	1 (2.6%)	0	0
Abdominal pain	8 (20.5%)	4 (10.3%)	0	0
Nausea/vomiting	6 (15.4%)	4 (10.3%)	0	0
Abdominal distension	5 (12.8%)	6 (15.4%)	0	0
Diarrhoea	2 (5.1%)	3 (7.7%)	0	0
Hypertension	5 (12.8%)	5 (12.8%)	10 (25.6%)	0
Hand-foot syndrome	9 (23.1%)	4 (10.3%)	5 (12.8%)	0
Oral ulcer	4 (10.3%)	2 (5.1%)	0	0
Proteinuria	2 (5.1%)	4 (10.3%)	3 (7.7%)	0
Sepsis	0	0	1 (2.6%)	0
Cholecystitis	0	1 (2.6%)	0	0

CTCAE Common Terminology Criteria for adverse events.

neutrophil count more than $1500/\text{mm}^3$, platelet count more than $75,000/\text{mm}^3$), (4) adequate renal function (serum creatinine up to 1.5 times the upper normal limit, (5) at least one measurable intrahepatic lesion as defined by RECIST 1.1. The main exclusion criteria included any loco-regional or systemic therapy within the last 4 weeks, previous exposure to apatinib, oxaliplatin or raltitrexed, and uncontrolled hypertension. More detailed inclusion and exclusion criteria are listed in the Study Protocol (in Supplementary Note 2 in the Supplementary Information).

Procedures

For the HAIC procedure, the Seldinger technique was used to puncture the femoral artery. Under the guidance of digital subtraction angiography, the catheter and coaxial microcatheter were inserted into the feeding hepatic artery. Specific details were shown in HAIC protocol (in the Supplementary Note 1 in the Supplementary Information). The treatment regimen was administered as follows: oxaliplatin, 85 mg/m^2 (continuous infusion for 4 h); raltitrexed, 3 mg/m^2 (continuous infusion for 1 h). After HAIC, the catheter and sheath were removed. The treatment was divided into 3-week cycles, with a maximum of 6 cycles, and continued until disease progression, intolerant toxicities, or patient withdrawal.

All patients were orally administered apatinib at an initial dose of 500 mg once daily for the first time 2 days after initial HAIC, and continued until disease progression, intolerant toxicities, or patient withdrawal.

Treatment modifications were allowed for the AE of apatinib and HAIC, including treatment interruption and dose reduction of apatinib and chemotherapeutic drugs. Repeated interruptions of treatment were permitted as required for no more than 14 days each time.

When grade 3 or 4 AE occurred during HAIC treatment, the next HAIC procedure was suspended until the AE decreased to grade 1 or

below; the HAIC procedure was resumed, and both chemotherapeutic drugs were reduced by 25%.

For grade 4 non-hematological AE, apatinib was delayed recovery to grade 1 or below, and then the dose was reduced once. When the first non-hematological AE of grade 3 and hematological AE of grade 3 or 4 occurred, apatinib was delayed until recovery to non-hematological AE of grade 1 or below and hematological AE of grade 2 or below, and then the treatment was resumed at the same dose. At the second occurrence of non-hematological AE grade 3 and hematological AE grade 3 or 4, the patient received a dose reduction (500 mg and 250 mg alternately or 250 mg once a day, depending on the dose level at the time of AE). If researchers considered to reduce the dose necessary, then reduce the dose for intolerable grade 2 AE.

Assessments

All patients were evaluated and documented within a week before the study. Abdominal contrast-enhanced CT or MRI and Chest CT were performed after two, four, and six cycles of HAIC during the combination stage of apatinib plus HAIC, and subsequently every 2 months during apatinib monotherapy until confirmed disease progression. During the combination stage, patients had to come to the inpatient every 3 weeks. During the apatinib monotherapy, patients had to come to the outpatient clinic every month. Two radiologists with more than 10 years of experience in liver cancer diagnosis independently compared the follow-up images with baseline images without survival data to evaluate best tumor response to treatment. Physical examination, tumor markers, blood tests, including hematologic, liver function and renal function tests, were performed when patients came to the inpatient or outpatient clinic as required, and any dysfunction was evaluated. For patients with suspected of new extrahepatic spread, further examination was performed. The AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Outcomes and endpoints

The primary endpoint was the ORR, which was calculated by dividing the number of patients with a best response of complete or partial response by the total number of patients. Tumor response was assessed according to the RECIST v1.1 and mRECIST. The secondary endpoints were PFS, disease control rate, 6- and 12-month survival rates, OS, and AEs. The PFS was calculated from the initiation of the first treatment to the date of disease progression or death by any cause, or it was censored on the last follow-up day if the patient was still alive. The disease control rate was calculated by dividing the number of patients with a best response of complete response, partial response, or stable disease for ≥ 6 weeks by the total number of patients. The 6- and 12-month survival rates were calculated as the proportion of surviving patients after 6 and 12 months, respectively. The OS was defined as the time from the initial treatment until death from any cause, or it was censored on the last follow-up day if the patient was still alive. The intrahepatic control period referred to the time from initial treatment to the progression of intrahepatic lesions. The extrahepatic control period referred to the time from initial treatment to the progression of extrahepatic lesions.

Statistics and reproducibility

We used Simon's two-stage design with a one-sided α error rate of 5% and a power of 80%³⁹. The null hypothesis that the true objective response rate per RECIST v1.1 was $\leq 30\%$ was tested against a one-sided alternative of $>30\%$. A true objective response rate of 50% was assumed. Under these assumptions, the study should be continued after the first stage if six or more enrolled patients responded out of the first 19. This study would be regarded as a success if 16 or more patients out of the total of 39 showed signs of response.

Categorical data were assessed using the chi-square test. The median PFS, OS and associated 95% CIs, and 6-month and 12-month survival rates were estimated using Kaplan–Meier survival analysis, and the median PFS of intrahepatic and extrahepatic lesions were compared using the log-rank test. All statistical analyses were performed using the SPSS software (version 23.0, IBM Corp., Armonk, NY).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The datasets generated during and/or analyzed during the current study are available in the Article and Supplementary Information and Source Data file. The de-identified participant data and statistical analysis plan may also be accessed from the first author Shiguang Chen (Email: sgchen207@163.com) within 3 months to 3 years after this article publication. And the data is only used for the research purpose. The HAIC protocol and study protocol are available in the Supplementary Information file under Supplementary Note 1 and 2, respectively. The remaining data are available in the manuscript, Supplementary Information, or Source Data file. Source data are provided with this paper.

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Competing interests

The authors declare no competing interests.

Additional information

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