

Efficacy and Safety of apatinib in patients with intermediate/advanced hepatocellular carcinoma: A prospective observation study

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Abstract

This prospective study aimed to evaluate the efficacy and safety of apatinib in patients with intermediate/advanced hepatocellular carcinoma (HCC).

The patients with intermediate/advanced HCC, who met predetermined inclusion and exclusion criteria, underwent oral treatment of apatinib 500 mg daily. The drug-related adverse effects were monitored by regular follow-up and workup including laboratory tests and imaging examinations. Tumor response was assessed by response evaluation criteria in solid tumor criteria. The time to tumor progression (TTP) and overall survival rate (OS) were calculated using the Kaplan–Meier method.

A total of 31 patients were enrolled in the study from October 28, 2015 to December 28, 2016. The number of patients with intermediate and advanced HCC was 4 (12.90%) and 27 (87.10%), respectively. The mean tumor size was 9.47 ± 5.48 cm (range: 1.2–19 cm). Vascular invasion was seen in 14 patients (45.16%). A total of 21 (67.74%) patients exhibited extrahepatic metastases. On the basis of first follow-up computed tomography and magnetic resonance imaging at 6 weeks after treatment, 10 (32.26%), 15 (48.39%), and 6 (19.35%) of 31 patients achieved a partial response, stable disease, and progression of disease, respectively. Response rate and disease control rate were 32.26% and 80.65%, respectively. The median TTP was 4.8 months (95% confidence interval: 3.75–5.86 months). Furthermore, 6- and 12-month OS rates were 73.8% and 55.4%, respectively. Grade 3 thrombocytopenia (6.45%) and hypertension (48.39%) were the most common hematologic and nonhematologic toxicities. Grade 3 elevation of either serum total bilirubin or aminotransferase (6.45%) was observed as the top incidence among important indexes of liver function.

Our preliminary findings suggest apatinib is a safe and effective therapy in intermediate/advanced HCC patients with high tumor response and survival rates.

Abbreviations: AASLD = American Association for the Study of Liver Disease, AFP = a-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CTCAE = Common Terminology Criteria for Adverse Events, EASL = European Association for the Study of Liver, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, OS = overall survival, IVC = inferior vena cava, PV = portal vein, RECIST = response evaluation criteria in solid tumor, RFA = radiofrequency ablation, SMV = superior mesenteric vein, TACE = transarterial chemotherapy embolization, TT = tumor thrombus, TTP = time to tumor progression, VEGFR-2 = vascular endothelia growth factor receptor-2.

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Authorship: Wen-Chang Yu designed this research and drafted the present manuscript; Kong-Zhi Zhang followed-up all patients during whole research period; Shi-Guang Chen and Wen-Chang Yu carried out the clinical study; Wei-Fu Liu collected and analyzed the data.

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1. Introduction

Hepatocellular carcinoma (HCC) is closely associated with liver cirrhosis. HCC is one of the five most common cancers worldwide and >50% of patients with HCC are found in China.^[1,2] According to Barcelona Clinic Liver Cancer (BCLC) system,^[3,4] liver transplantation, surgical resection, and radiofrequency ablation (RFA) are radical treatments for patients with early stage HCC, which yield 5-year survival rates of about 70%–79%, 41.3%–69.5%, and 40%–70%, respectively.^[5–8] Unfortunately, the majority of patients present at an intermediate or advanced stage at diagnosis; therefore, they are not suitable for the above-mentioned radical procedures. Transcatheter arterial chemoembolization (TACE) is a recommended treatment option for intermediate stage (BCLC stage B) HCC. Two randomized trials from Europe and Asia have confirmed a survival benefit after TACE compared with that after conservative treatment.^[9,10] Although there is an agreement on increased tumor response, the survival benefit after TACE is possibly limited to a subgroup of patients with preserved liver function and limited disease.^[11] Some patients with intermediate stage HCC were

usually presumed to have little chance of survival benefit from TACE treatment due to intrahepatic diffusion lesions or the presence of arteriportal shunts. All locoregional treatment modalities including TACE are not preferred options for the patients with advanced (BCLC stage C) HCC due to the presence of extrahepatic metastases or vascular invasion.

Effective systemic treatment should be preferentially considered for all advanced and some intermediate HCC patients. The systemic chemotherapy for advanced HCC has been administered for many years. Although the efficacy is gradually improved with the use of novel chemotherapy agents in clinical practice, the recent randomized trial showed the patients with advanced HCC did not receive significant survival benefit from the chemotherapy with a median overall survival (OS) of only 6.4 months.^[12] Both the SHARP and ORIENTAL studies demonstrated an OS improvement of nearly 3 months for sorafenib compared with the best supportive care in patients with advanced HCC^[13,14]; thus, sorafenib was recommended as the standard first-line therapy for advanced HCC in terms of BCLC system.^[3,4] However, it is a common fact that most patients with HCC cannot afford the high cost of sorafenib and have declined treatment with the molecular targeted agent. It is necessary to explore affordable molecular targeted agents for patients with intermediate/advanced HCC.

Apatinib (Hengrui Pharmaceutical Co., Ltd, Shanghai, People's Republic of China) is a small-molecule tyrosine kinase inhibitor that highly and selectively inhibits vascular endothelial growth factor receptor (VEGFR)-2, leading to inhibition of vascular endothelial growth factor (VEGF)-mediated endothelial cell migration and proliferation and decrease in tumor microvascular density. As one of the latest generation of orally antiangiogenic agents, apatinib was approved in People's Republic of China in 2014 as a subsequent-line treatment for patients with advanced gastric cancer. In addition, it is currently undergoing phase II/III clinical trials in multiple tumor types, such as nonsmall-cell lung cancer, breast cancer, and HCC.^[15,16] Pilot studies demonstrate that apatinib has potential antitumor activity across a broad range of advanced solid tumors.^[17,18] Because of the dilemma of having no alternative treatment options, some patients with intermediate/advanced stage HCC accepted oral apatinib treatment from October 28, 2015 in our institution. We prospectively scheduled the follow-up and clinical observation for all patients. In this study, we aimed to evaluate efficacy and safety of apatinib in patients with intermediate/advanced HCC.

2. Methods

2.1. Patients and patient's selection criteria

This study was approved by the institutional review board of Fujian Cancer Hospital Ethics Committee and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Informed consents were obtained from all patients before enrolment. Inclusion criteria for this study were as follows: (a) Patients who were diagnosed as having HCC based on American Association for the Study of Liver Disease and European Association for the Study of Liver HCC management guidelines^[3,4]; (b) Patients who had received previous locoregional treatments, such as external beam radiotherapy, TACE, RFA, were eligible for enrolment in the study, provided that either the target lesion showed progression of disease or the target lesion

had not been treated with locoregional therapy. In addition, the locoregional therapy must have ended more than 4 weeks before study entry. Patients with recurrent disease after previous resection were considered eligible for the study. The tumor staging was assessed according to the disease condition at the beginning of oral administration of apatinib; (c) BCLC stage C HCC patients with extrahepatic metastases and/or vascular invasion; BCLC stage B HCC patients with intrahepatic multiple lesions and/or concomitant arteriportal shunts; (d) ages 18–70 years; (e) acceptable functions of bone marrow (hemoglobin ≥ 10 g/dL, white blood cell $\geq 3000/\mu\text{L}$, platelet count $\geq 50000/\mu\text{L}$), liver (bilirubin ≤ 3 mg/dL, aminotransferase ≤ 200 U/L), and renal (creatinine ≤ 390 $\mu\text{mol/L}$); (f) performance status of ≤ 2 . Exclusion criteria were as follows: (a) decompensated liver disease (ascites not controlled with diuretics; encephalopathy, active or recent [2 weeks] gastrointestinal bleeding); (b) active infection or sepsis; (c) pregnancy; (d) heart insufficiency, severe pulmonary dysfunction; (e) the life expectancy less than 3 months.

2.2. Treatment plan, drug dose adjustment

Upon agreeing to participate in the study, patients were immediately prescribed two tablets of apatinib (250 mg tablet) once daily. When the patients encountered grade 3–4 drug-related adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, the drug dose was adjusted to one tablet or interrupted for several days. After adverse events were relieved, the patients were recommended to resume two tablets of apatinib every day. Treatment continued until patient's death, significant disease progression, drug intolerance, or withdrawal of consent from the study.

2.3. Follow-up schedule, tumor response assessment, and survival time

All patients were regularly followed-up in our institution by scheduled protocol. Every patient received a thorough inquiry about adverse events, physical examination, and laboratory tests including hepatorenal function, blood routine, and urine routine every 2 weeks. The first upper abdominal enhanced magnetic resonance imaging (MRI) and chest computed tomography (CT) were planned to evaluate tumor response at the time of 6 weeks after treatment, and then the above-mentioned scans were performed at an approximate 8-week interval. The follow-up was still ongoing even after the last patient enrolment. Tumor response was determined according to response evaluation criteria in solid tumor (RECIST criteria).^[19] Time to tumor progression (TTP) was defined as the time between administration of apatinib and the time that tumor progression was diagnosed. OS referred to the time from administration of apatinib to patient's death by any cause or the last follow-up.

2.4. Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as number and percentage, and continuous variables were expressed as mean \pm standard deviation (SD) or median and interquartile range when appropriate. Kaplan–Meier survival curve was used to examine TTP and OS. All statistical tests were two-sided. $P < 0.05$ was considered statistically significant.

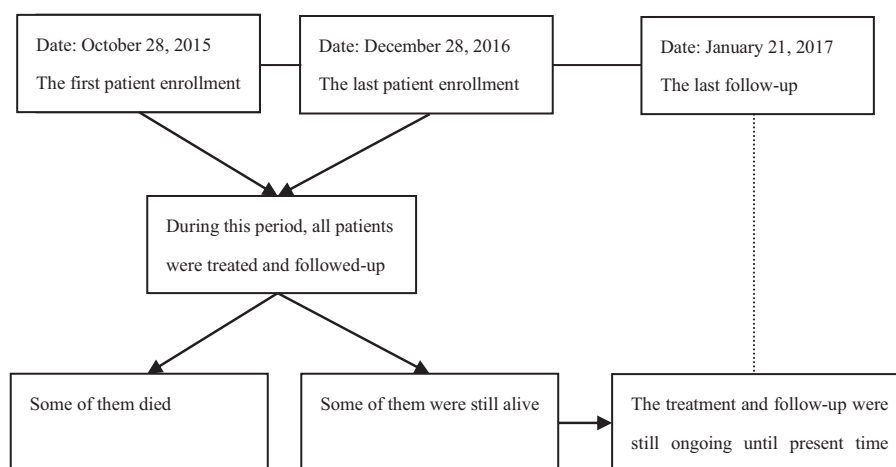


Figure 1. Patients' enrolment and outcomes (flow chart).

3. Results

A total of 31 patients were enrolled in the study from October 28, 2015 to December 28, 2016. The date of the last follow-up was January 21, 2017. The research flow chart is presented in Figure 1.

3.1. Clinical profiles of patients

The clinical profiles of the study population are shown in Table 1. A total of 31 patients (26 men, 5 women) had a mean age of 46.26 ± 11.78 years (range: 24–70 years). Hepatitis B virus infection was seen in 31 (100%) patients. Of all patients, 23 (74.19%) patients had Child–Pugh A and 8 (25.81%) with Child–Pugh B cirrhosis. The mean tumor size was 9.47 ± 5.48 cm (range: 1.2–19 cm). A total of eight (25.81%) patients had tumor size of ≤ 5 cm and 23 (74.19%) had tumor size of > 5 cm. The number of tumors in eight (25.81%) patients was ≤ 3 , whereas the number of tumors in 23 (74.19%) patients was > 3 . Vascular invasion was seen in 14 patients (45.16%); among which 6 (19.35%) showed tumor thrombus (TT) in the first-order branch of portal vein (PV) or further, 5 (16.13%) TT in the main PV only, 1 (3.22%) TT in the main PV and inferior vena cava, and 2 (6.45%) TT in the main PV and superior mesenteric vein. A total of 21 (67.74%) patients exhibited extrahepatic metastases. Metastatic sites of all patients included the bone (2 cases, 6.45%), lung (11 cases, 35.48%), lymph node (14 cases, 45.16%), and adrenal gland (1 case, 3.23%). Of 31 patients, 11 (35.48%) had serum AFP < 200 ng/mL and the remaining 20 (64.51%) had AFP ≥ 200 ng/mL. The number of patients with BCLC stage B/C HCC was 4 (12.90%) and 27 (87.10%), respectively. A total of 25 (80.65%) patients had received prior locoregional therapies including external beam radiotherapy, radical resection, radiofrequency ablation, and transarterial chemotherapy embolization before the apatinib treatment. Every patient (100%) underwent either reduction or interruption of apatinib dose due to drug-related adverse events. Thirteen (41.94%) patients had already permanently discontinued the oral apatinib due to death or tumor progression, with a mean duration time of taking apatinib for 4.46 ± 3.10 months (range: 1.5–12.5 months). The remaining 18 (58.06%) patients still took oral apatinib, with a mean duration of oral apatinib for 6.56 ± 3.74 months (range: 1.8–13.3 months) until the last follow-up, January 21, 2017.

Table 1

Baseline clinical characteristics of patients.

Characteristics	Value
Age (years)	
Mean \pm SD	46.26 \pm 11.78
Range	24–70
Gender, n (%)	
Male	26 (83.87)
Female	5 (16.13)
Etiology, n (%)	
HBV	31 (100)
Child–Pugh class, n (%)	
A	23 (74.19)
B	8 (25.81)
Tumor size (cm), n (%)	
Mean \pm SD	9.47 \pm 5.48
≤ 5 cm	8 (25.81)
> 5 cm	23 (74.19)
Number of tumors, n (%)	
1–3	8 (25.81)
> 3	23 (74.19)
Vascular invasion, n (%)	
TT in the first-order branch of PV or further	6 (19.35)
TT in the main PV only	5 (16.13)
TT in the main PV and IVC	1 (3.22)
TT in the main PV and SMV	2 (6.45)
Metastatic sites, n (%)	
Bone	2 (6.45)
Lung	11 (35.48)
Lymph node	14 (45.16)
Adrenal gland	1 (3.23)
AFP, n (%)	
< 200 ng/mL	11 (35.48)
≥ 200 ng/mL	20 (64.51)
BCLC stage, n (%)	
B	4 (12.90)
C	27 (87.10)
Efficiency after prior treatment*, n (%)	
The targeted lesions progression	17 (54.84)
New lesions presentation	5 (16.13)
The remaining lesions	3 (9.68)

AFP = alpha-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, HBV = hepatitis B virus, IVC = inferior vena cava, PV = portal vein, SMV = superior mesenteric vein, TT = tumor thrombus.

* Prior therapies refer to external beam radiotherapy, radical resection, radiofrequency ablation, transarterial chemotherapy embolization, and percutaneous ethanol injection.

3.2. Tumor response rate, TTP, and OS

In the analysis for tumor response on the basis of first follow-up CT and MRI at 6 weeks after treatment, 10 (32.26%) of 31 patients achieved a partial response and 15 (48.39%) and 6 (19.35%) of 31 patients achieved stable disease and progression disease, respectively. Response rate and disease control rate were 32.26% and 80.65%, respectively. During a mean follow-up period of 6.38 ± 3.63 months (range: 1.8–14 months), 8 patients died of tumor progression or liver failure without deaths being categorized as drug-related, and 23 were alive at the last follow-up. The median TTP was 4.8 months (95% confidence interval [CI]: 3.75–5.86 months) (Figure 2). Furthermore, Kaplan–Meier survival curve analysis showed that 6- and 12-month OS rates were 73.8% and 55.4%, respectively (Figure 3).

3.3. Adverse effects

No grade 4 or 5 toxicities occurred in all patients. Table 2 summarizes the incidence of all grades 1–3 toxicities observed based on the CTCAE during oral apatinib treatment. Among the nonhematologic toxicities, the most commonly observed grade 3 adverse effect was hypertension (48.39%). Grade 3 thrombocytopenia was the most common hematologic toxicity (6.45%). Grade 3 elevation of either serum total bilirubin or aminotransferase (6.45%) was observed as the top incidence among important indexes of liver function. All toxicities were manageable by adjusting the drug dose and providing symptomatic treatment.

4. Discussion

Angiogenesis is mediated by VEGF and plays an important role in the process of tumor growth.^[20] VEGFRs are tyrosine kinases functioning as key regulators of angiogenesis. VEGFR family proteins are membrane receptor tyrosine kinases, including VEGFR-1, VEGFR-2, and VEGFR-3.^[21] VEGFR-2, which is

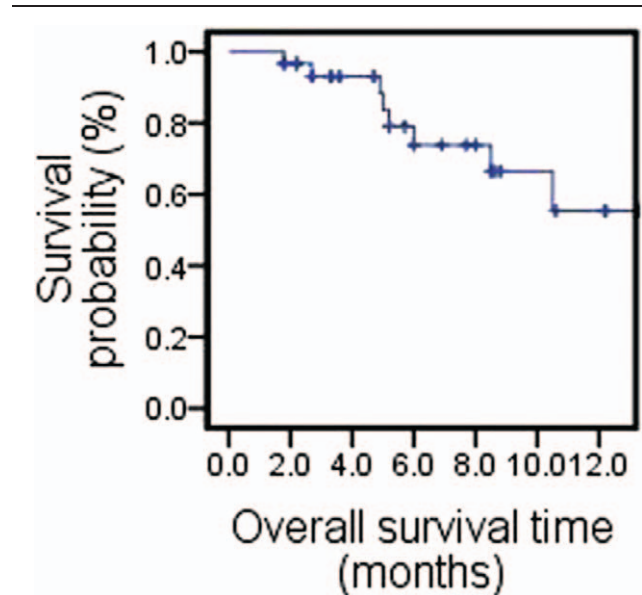


Figure 3. Overall survival probability of all patients ($n=31$). 6- and 12-month overall survival rates were 73.8% and 55.4%, respectively.

mainly expressed on endothelial cells, mediates angiogenic, mitogenic, and permeability-enhancing effects of VEGF. Apatinib is the latest inhibitor of VEGFR-2 targeting the intracellular Adenosine triphosphate-binding site of the receptor, which could inhibit VEGF-stimulated endothelial cell migration and proliferation, decrease tumor microvascular density, and promote apoptosis. The results from a phase III trial of apatinib in patients with advanced chemotherapy-refractory metastatic gastric carcinoma demonstrated that median OS and progression-free survival were significantly improved in the apatinib group compared with the placebo group (6.5 vs 4.7 months; 2.6 vs 1.8 months; $P < 0.05$).^[22]

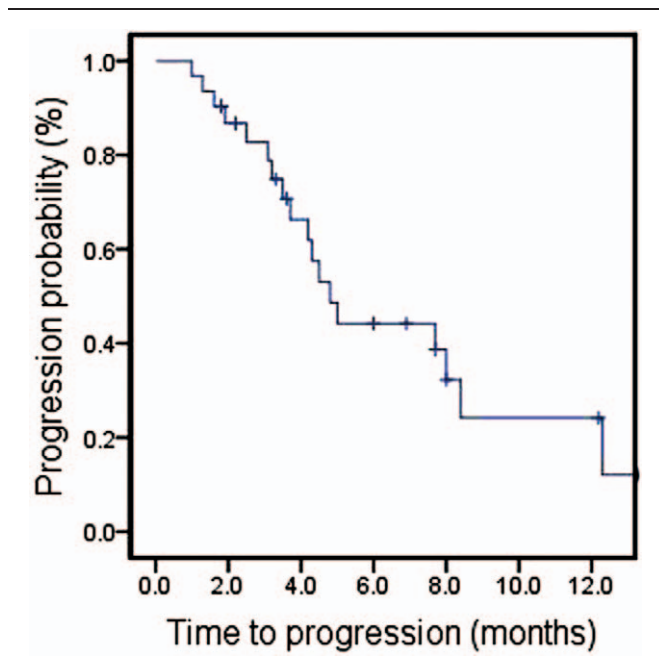


Figure 2. Progression probability of all patients ($n=31$). Median time to progression was 4.8 months (95% CI: 3.75–5.86 months).

CTCAE grade	I, n (%)	II, n (%)	III, n (%)
Nonhematologic			
Fatigue	14 (45.16)	11 (16.03)	6 (19.35)
Vomiting	3 (23.08)	7 (22.58)	
Diarrhea	2 (6.45)	7 (22.58)	
Hypertension		7 (22.58)	15 (48.39)
Hand-foot syndrome	5 (16.13)	13 (41.93)	13 (41.93)
Oral ulcer		1 (3.23)	4 (12.90)
Hoarseness		3 (9.68)	
Upper gastrointestinal bleeding			1 (3.23)
Perianal ulceration		2 (6.45)	
Proteinuria	2 (6.45)	4 (12.9)	4 (12.90)
Liver function			
Serum albumin reduction	5 (16.13)	12 (38.71)	
Serum total bilirubin elevation	1 (3.23)	8 (25.81)	2 (6.45)
Serum aminotranferase elevation	4 (12.90)	6 (19.35)	2 (6.45)
Hematologic			
Anemia		2 (6.45)	
Leukopenia	4 (12.9)	6 (19.35)	1 (3.23)
Thrombocytopenia	3 (9.68)	6 (19.35)	2 (6.45)

CTCAE=Common Terminology Criteria for Adverse Events.

In our study, 45.16% of all patients had vascular invasion and 67.74% had extrahepatic metastases. Furthermore, the majority (80.65%) of patients had progressive, recurrent, and remaining lesions after undergoing a variety of locoregional therapies. It was tough to select a subsequent treatment option for this population of patients with fairly complicated HCC. Even though sorafenib is recommended as a standard therapy for patients with advanced HCC, it results in a benefit of only 2–3 months in the OS or TTP according to the phase III clinical study.^[13,14] The results of a phase II clinical study showed that apatinib was efficient as the first-line therapy for patients with advanced HCC.^[23] In this study, patients with advanced HCC were randomized into two groups in which they received 850 mg or 750 mg apatinib daily respectively until progression of tumor. The TTPs were 4.21 and 3.32 months in 850 mg and 750 mg groups ($P > 0.05$), respectively. Based on high incidences of adverse events (hypertension, 49.02%; proteinuria, 47.06%; hand-foot syndrome, 29.41%) observed in the 750 mg group, the dose of daily apatinib was adjusted to 500 mg in our study. In the present study, tumor response rate and disease control rate were far higher (32.26% and 80.65%) than the results from ORIENTAL study (3.3% and 35.3%).^[14] Lim et al.^[24] recently reported that the tumor response rate and disease control rate were only 6.2%, 44.8%, respectively, in Asian patients with unresectable hepatocellular carcinoma treated with refametinib and sorafenib. This implies that apatinib may produce significant antitumor effects in the short term in most patients with advanced HCC. The median TTP was 4.8 months, and 6- and 12-month OS rates were 73.8% and 55.4%, respectively, in our study. The patients in our study had a longer median TTP and higher 6-month OS rate compared with TTP (2.8 months) and 6-month OS rate (53.3%) in the ORIENTAL study.^[14] Although these are not head-to-head comparisons, it still suggests a trend of favoring apatinib efficiency in HCC.

Like other molecular targeted agents, various adverse events occurred during oral apatinib treatment in clinical practice. Moreover, significant individual differences were also found in our study. However, no grade 4 adverse events were observed. The three most common grade 3 events were hypertension (48.39%), hand-foot skin reactions (41.93%), and fatigue (19.35%), which were far higher in comparison with the incidences of grade 3/4 events reported in ORIENTAL study (2.0%, 10.7%, 3.4%, respectively).^[14] Although the drug-associated adverse events occurred in a significant proportion of patients, these adverse events gradually subsided because every patient was provided with full guidance during the treatment and no deaths were considered to be drug related. Our findings indicate that adverse events associated with apatinib are more common and severe in comparison with those related to sorafenib. However, with adequate help and timely dose adjustments, all patients still well-tolerated drug treatment. A preliminary study showed phosphorylated VEGFR-2 and hypertension were independent predictive factors for both progression-free survival and clinical benefit rate in advanced breast cancer patients with apatinib treatment.^[25] Yet, there is little understanding about the correlation of apatinib adverse effects and efficacy in patients with advanced HCC. McGlynn et al.^[26] reported that the greatest disparity in incidence occurs in Central European countries, where some registries have rates among males 4- to 5-fold higher than rates among females. The number of male patients (26 cases) was more than that of female patients (5 cases) in our study sample. There has even been a study to indicate that men treated with sorafenib had higher

survival rates than women.^[27] We are not sure if this trend existed similarly in our study because we did not perform a multivariate analysis to identify independent risk factors for survival due to a small study population.

This pilot study has several major limitations. Our study population was small and follow-up periods were relatively short. A single arm study prevented comparisons with other molecular targeted agents or a control group. Also, the present study did not observe how drug-related adverse effects influence patients' quality of life. Further prospective studies with a larger number of patients are warranted to prove that apatinib can be a highly recommended, standard first-line molecular targeting agent that supplements our findings.

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