Original Article

Adjuvant apatinib treatment after resection of hepatocellular carcinoma with portal vein tumor thrombosis: a phase II trial

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Background: Survival after resection of hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) still remains poor. Apatinib, a vascular endothelial cell growth factor receptor 2 inhibitor, has been shown to be safe and effective in patients with advanced HCC, so in the present study its efficacy and safety in the adjuvant setting was explored.

Methods: In this single-center, open-label phase II trial, the patients received apatinib (500 mg/day) until they experienced disease recurrence or intolerable toxicity. The primary endpoint was recurrence-free survival (RFS); the secondary endpoints included overall survival (OS) and safety.

Results: From a total of 49 patients who were screened between August 2017 and December 2018, 30 study participants received apatinib. According to the Liver Cancer Study Group of Japan classification of PVTT, there were 7, 11, and 12 participants with Vp1, Vp2, and Vp3, respectively. The median duration of treatment was 4.8 months [interquartile range (IQR): 2.0–8.8], and the median dose of apatinib was 339.7 mg/day (IQR: 267.7–500 mg/day). The median follow-up was 14.3 months (IQR: 12.3–19.3). The median RFS was 7.6 months [95% confidence interval (CI): 5.7–9.5 months]. The 1-year RFS rate and the 1-year OS rate were 36.1% and 93.3%, respectively. A total of 29 (96.7%) patients experienced adverse events, and 14 (46.7%) had grade 3 or 4 adverse events. No treatment-related deaths occurred.

Conclusions: Apatinib was well tolerated in patients after resection of HCC with PVTT. The median RFS in this group was improved compared with that previously reported.

Trial registration: No.: NCT03261791 (ClinicalTrials.gov).

Keywords: Apatinib; hepatocellular carcinoma (HCC); portal vein

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Introduction

Liver cancer is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide (1). Hepatocellular carcinoma (HCC) is the most common type of liver cancer (75–85%) (2), and the main treatment includes liver transplantation, liver resection, loco-regional therapy, and systemic therapy (2).

In China, 23% of patients with diagnosed HCC also have portal vein tumor thrombosis (PVTT) (3), which is an

indicator of an advanced stage and a poor prognosis (4-6). Untreated patients with HCC and PVTT have a median survival of about 2.7–4.0 months. Chinese Liver Cancer Treatment Guidelines recommend surgical resection, systemic treatment, transarterial chemoembolization, and radiation therapy for the treatment of HCC with PVTT (7). On the other hand, the American Association for the Study of Liver Diseases only recommends systemic treatment for HCC patients with PVTT (8).

Surgical resection can improve the survival of selected patients with HCC and PVTT, but has been associated with a high incidence of tumor recurrence (5,6). Total resection of liver cancer tissue and tumor thrombus is very challenging, especially for small tumor thrombus and micro-metastasis. Wei *et al.* suggested a 1-year recurrence-free survival (RFS) rate of 14.9% and 1-year overall survival (OS) rate of 43.1% in patients who underwent hepatectomy (9). Other studies have reported a 1-year RFS rate of 31.7% and a median RFS of 4.1 months in patients with PVTT who underwent hepatectomy (6,10). Postoperative adjuvant therapy might also improve patients' survival after hepatectomy.

Angiogenesis is involved in tumor growth and metastasis, and is an important factor in the control of HCC progression. Apatinib is a vascular endothelial growth factor receptor-2 inhibitor that has shown potent antitumor activity and good safety in a variety of solid tumors (11-13), including advanced HCC (14-16). Therefore, it might be a therapeutic option for controlling recurrence after resection of HCC with PVTT. Previous study evaluated an anti-angiogenic therapy, i.e., sorafenib, for patients with relatively low risk of recurrence with a negative result (STORM study). In the present study, we evaluated the efficacy and safety of adjuvant apatinib treatment in patients with HCC and PVTT, an indicator of a high risk of recurrence, after R0 resection, as a novel option for the management of such patients, who otherwise might face a poor prognosis. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6181).

Methods

Study design and ethical statement

This single-center, open-label phase II trial was carried out at Zhongshan Hospital, Fudan University, China. The study was supported by Hengrui Co. Ltd., and registered at ClinicalTrials.gov (#NCT03261791). The sponsor collaborated with authors on the study design, but the authors collected and analyzed the data, and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Ethics Committee of Zhongshan Hospital (No. B2017-065R). Informed consent was given by all individual participants.

Participants

The eligibility criteria were: (I) 18–70 years of age; (II) pathologically proven HCC based on the surgically resected specimen; (III) liver resection with curative intention; (IV) PVTT assessed by preoperative imaging or intraoperative findings within 4 weeks of surgery; (V) no preoperative antitumor treatment; (VI) Eastern Cooperative Oncology Group performance status score of 0 or 1; (VII) Child-Pugh score of A or B7; (VIII) adequate organ function, defined as hemoglobin ≥90 g/L, platelets $\geq 80\times10^9$/L, total bilirubin ≤1.5 × the institutional upper limit of normal (ULN), alanine transaminase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN, and serum creatinine ≤1.5 × ULN; and (IX) expected survival ≥6 months.

The key exclusion criteria were: (I) tumor invasion into intrahepatic or extrahepatic bile ducts, combined hepatocellular cholangiocarcinoma, or fibrolamellar HCC; (II) uncontrolled hypertension; and (III) medical history of myocardial ischemia, myocardial infarction, or arrhythmia.

Treatment

The patients received apatinib monotherapy until they experienced disease recurrence or intolerable toxicity occurred. Apatinib was given orally (500 mg/day) each day, during a cycle of 4 weeks. Dose adjustments, including interruptions and reductions, were allowed for the management of treatment-related adverse events (AEs). Follow-up imaging examinations (abdominal contrast-enhanced magnetic resonance imaging or computed tomography (CT) and chest CT were performed every 2 months or when tumor recurrence was suspected based on elevated serum levels of tumor biomarkers. Complete blood count, liver and renal function tests, serum tumor marker levels, and urine dry chemical analysis were also performed every 2 months during treatment and 1 month

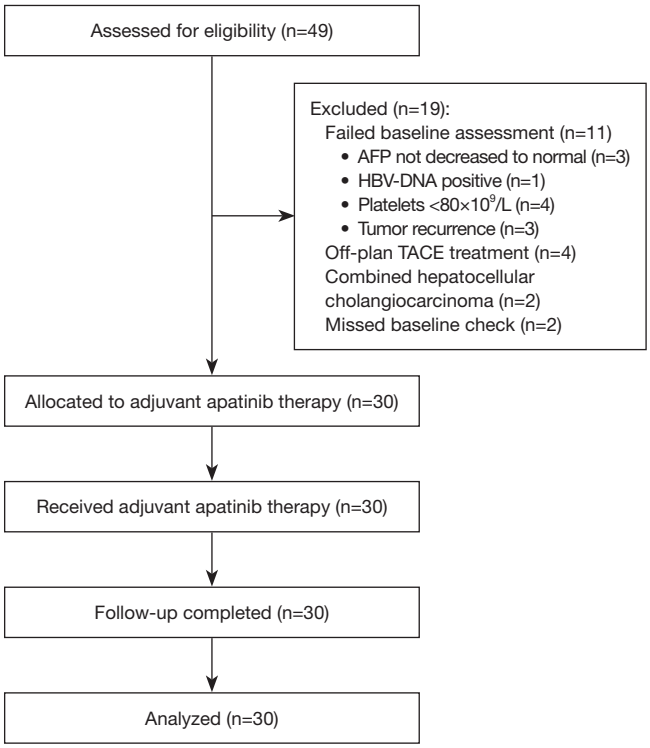

Figure 1 Patient flowchart. AFP, alpha-fetoprotein; HBV, hepatitis B virus; TACE, transarterial chemoembolization.

after discontinuation of treatment.

Assessment

The primary endpoint was RFS; tumor recurrence was determined by the investigators. RFS was defined as the time interval from liver resection to the diagnosis of intrahepatic relapse or distant metastasis, or death from any cause. The secondary endpoints included OS and safety. OS was defined as the time from HCC surgery to death from any cause. AEs were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The investigators assessed the relationship between treatment and AEs. All the AEs reported in this study were treatment-related AEs per investigator assessment.

Statistical analysis

This was an exploratory study to preliminarily evaluate the efficacy and safety of apatinib as adjuvant treatment in patients who underwent R0 resection for HCC and PVTT; therefore, a small sample size of 30 was planned. The efficacy analyses were conducted on the intent-to-treat (ITT) population, which was defined as patients who received at least 1 dose of the study drug. The Kaplan-Meier product-limit method was used to estimate the median times of RFS and OS in the ITT population. AEs and serious AEs were analyzed in patients who received at least 1 dose of the study drug. Only descriptive statistics were used. Quantitative variables were shown as mean ± standard deviation or median [interquartile range (IQR)].

Results

Participant enrollment and baseline characteristics

Among a total of 49 patients who were screened between August 2017 and December 2018, 30 participants received apatinib (*Figure 1*). On February 27, 2020, 3 patients were still receiving apatinib treatment at a dosage of 250 mg/d. The baseline characteristics of the 30 participants (ITT population) are presented in *Table 1*. The median age was 55 years (IQR: 49–62 years), and 25 (83.3%) patients were male. According to the Liver Cancer Study Group of Japan (LCSGJ) classification of PVTT (17), there were 7 (23.3%), 11 (36.7%), and 12 (40.0%) participants with Vp1, Vp2, and Vp3, respectively.

Apatinib treatment

The median follow-up was 14.3 months (IQR: 12.3–19.3), and the median duration of treatment was 4.8 months (IQR: 2.0–8.8) (*Table 2*). The median dose of apatinib was 339.7 mg/d (IQR: 267.7–500 mg/d), and the median total drug exposure was 57.2 g (IQR: 25.8–78.8 g).

Efficacy

For patients with HCC and PVTT, the median RFS was 7.6 months [95% confidence interval (CI): 5.7–9.5 months]. The 1-year RFS rate was 36.1%, and the 1-year OS was 93.3% (*Table 2*, *Figure 2*).

Safety

During the treatment period, 29 (96.7%) patients experienced AEs of any grade, and 14 (46.7%) experienced grade 3 or 4 AEs. The treatment-related AEs are listed in *Table 3*. No treatment-related deaths occurred. The most

Table 1 Characteristics of the participants

Characteristics	Values (n=30)
Age, median [range], years	55 [49–62]
Sex (male/female)	25/5
HBsAg (positive/negative)	26/4
Tumor size, mean ± SD, cm	7.2±2.6
No. of lesions (1/≥2/≥3)	24/6
Type of portal vein thrombosis (Vp1/Vp2/Vp3)[†]	7/11/12
α-fetoprotein, median (IQR), ng/mL	179.5 (15.9–3,460.5)
Protein induced by vitamin K absence, median (IQR), mAU/mL	978.5 (212.0–8,113.0)
Total bilirubin, mean ± SD, μmol/L	13.9±6.0
Alanine transaminase, mean ± SD, U/L	41.0±24.7
Albumin, mean ± SD, g/L	43.8±3.8
γ-glutamyl transferase, mean ± SD, U/L	96.2±63.1
International normalized ratio, mean ± SD	1.0±0.1
Hemoglobin, mean ± SD, g/L	145.4±16.3
Platelets, mean ± SD, $\times 10^9$/L	154.0±66.1
Leukocytes, mean ± SD, $\times 10^9$/L	4.9±1.9

[†], based on the Liver Cancer Study Group of Japan (LCSGJ) classification. IQR, interquartile range; SD, standard deviation.

Table 2 Efficacy evaluation

Variables	Values
Median follow-up (months), median (IQR)	14.3 (12.3–19.3)
Median duration of treatment (months), median (IQR)	4.8 (2.0–8.8)
Median RFS (months) (95% CI)	7.6 (5.7–9.5)
1-year RFS rate (%)	36.1
1-year OS rate (%)	93.3

IQR, interquartile range; LCSGJ, Liver Cancer Study Group of Japan; OS, overall survival PVTT, portal vein tumor thrombosis; RFS, recurrence-free survival.

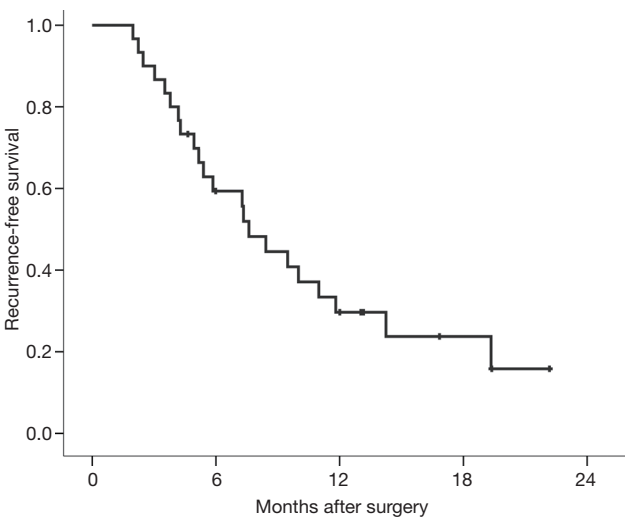

Figure 2 Recurrence-free survival after surgery.

common treatment-related AEs were thrombocytopenia (n=16, 53.3%), hand-foot syndrome (n=14, 46.7%), neutropenia (n=13, 43.3%), hypertension (n=9, 30.0%), increased ALT (n=7, 23.3%), and hoarseness (n=7, 23.3%).

Treatment-related grade 3 or 4 AEs included thrombocytopenia (n=5, 16.7%), neutropenia (n=4, 13.3%), proteinuria (n=3, 10.0%), hypertension (n=3, 10.0%), increased ALT (n=1, 3.3%), increased AST (n=1, 3.3%), diarrhea (n=1, 3.3%), upper gastrointestinal hemorrhage (n=1, 3.3%), hoarseness (n=1, 3.3%), and hand–foot syndrome (n=1, 3.3%) (*Table 3*). The patient with gastrointestinal bleeding and hepatic encephalopathy

Table 3 Treatment-related adverse events

Treatment-related adverse events	All grades, n (%)	Grade 3 or 4, n (%)
Any adverse event	29 (96.7)	14 (46.7)
Thrombocytopenia	16 (53.3)	5 (16.7)
Neutropenia	13 (43.3)	4 (13.3)
Proteinuria	4 (13.3)	3 (10.0)
Hypertension	9 (30.0)	3 (10.0)
ALT increased	7 (23.3)	1 (3.3)
AST increased	3 (10.0)	1 (3.3)
Diarrhea	3 (10.0)	1 (3.3)
Upper gastrointestinal hemorrhage	1 (3.3)	1 (3.3)
Hoarseness	7 (23.3)	1 (3.3)
Palmar-plantar erythrodysesthesia syndrome	14 (46.7)	1 (3.3)
Anorexia	4 (13.3)	0
Headache	3 (10.0)	0
Dizziness	2 (6.7)	0
Fatigue	2 (6.7)	0
Periodontal disease	1 (3.3)	0

ALT, alanine transaminase; AST, aspartate aminotransferase.

was relieved of symptoms after drug withdrawal and hospitalization.

Discussion

Patients with HCC and PVTT have a poor prognosis. Because apatinib has been shown to be safe and effective in several solid tumors, including HCC, we conducted the first trial, to the best of our knowledge, evaluating the efficacy and safety of an anti-angiogenesis agent in patients with HCC and PVTT after R0 resection. The results showed that adjuvant apatinib had good treatment efficacy with a tolerable safety profile in these patients.

Previous studies have verified the efficacy of a dose of 500–850 mg/day of apatinib in patients with various solid tumors (11-13,18-26). Moreover, meta-analyses showed that the objective response rate and disease control rate were higher with the 850 and 750 mg/day dosages than with a lower dose (18-26). Most recently, apatinib 750 mg/day showed improved OS in comparison with placebo in a phase III clinical trial when used as second-line therapy in patients with a progressed tumor or those intolerant to previous systemic chemotherapy and/or sorafenib (27). Considering that previous studies have reported 77.4% treatment-related AEs of grade 3 or 4 (28), we chose a lower dosage for apatinib in the adjuvant setting. In this study, apatinib 500 mg/day was well tolerated, and there was 46.7% treatment-related AEs of grade 3 or 4.

Recent studies that included Eastern Asian patients suggested that surgical resection could be a treatment option for patients with Barcelona Clinic Liver Cancer (BCLC) C stage HCC, especially those with type I or II PVTT. Peng *et al.* (29) found a 1-year RFS and OS of 63.0% and 81.5%, respectively, in HCC patients with type I PVTT, and 20.9% and 46.3%, respectively, for type II PVTT among those who underwent hepatic resection for HCC. Kokudo *et al.* (30) examined patients with R1 or R2 resection, reporting a favorable long-term survival after resection with median RFS and OS for Vp1, Vp2, and Vp3 of 1.23 and 4.13 years, 0.82 and 2.49 years, and 0.56 and 1.58 years, respectively. Moreover, Zhang *et al.* (31) showed that for patients with type I or II PVTT and R0 resection (type I PVTT represented 34–48.7% of the patients), the median RFS was 4.9–8.1 months, and median OS was 9.3–10.4 months. In a group of patients with predominantly type I PVTT (>90%), the median RFS and OS were 11.0

and 12.4 months, respectively. Therefore, the extent of PVTT is associated with survival in patients with HCC. Patients with more extensive PVTT possibly have a larger residual lesion after surgery, and in those cases, adjuvant apatinib might be an option.

In the present study, the 1-year (36.1%) and median RFS (7.6 months), and 1-year OS (93.3%) were higher than in a previous study that recruited similar participants randomized to surgery (1-year OS, 43.1%) versus surgery plus radiation therapy (1-year OS, 75.2%) (9). These differing results could be partly explained by that the patients recruited in the present study had a better performance status than previous study, but also by the use of apatinib, which needs to be examined in a controlled trial. Nevertheless, the OS was substantially longer than the 8.9 months and 5.6 months (HCC with macrovascular invasion and/or extrahepatic spread) reported by the SHARP (32) and Asia-Pacific (33) trials, respectively, for sorafenib monotherapy. In addition, a small-series study reported that adjuvant sorafenib after HCC resection improved the time to progression and OS compared with surgery alone in patients with HCC and PVTT (34). Patients with adjuvant sorafenib therapy had an improved time to progression (29 *vs.* 22 months, P=0.041) and an improved OS (37 *vs.* 30 months, P=0.01).

Anti-angiogenesis targeted therapy has been shown to delay wound healing (35), so in the present trial, apatinib was started 4–6 weeks after surgery to ensure safety. The occurrence of grade 3 or 4 AE was, in general, comparable to that in the STORM trial conducted with patients who received sorafenib after HCC resection (i.e., 50% for grade 3 AEs and 2% for grade 4) (36). The most common apatinib-related AEs were hypertension and proteinuria, consistent with the known toxicity profile (11,14,15,18-20, 22-24,26). No new toxicity signals were identified.

There are some limitations to the present study that need to be pointed out. This was a single-arm exploratory trial without a control group or randomization and the sample size is small. Thus, the results are not conclusive. In future study, we should introduce a control group with standard treatment in clinical practice (e.g., TACE). Nevertheless, our results revealed a high RFS and 1-year OS, suggesting that further studies on apatinib for HCC and PVTT might be warranted.

Conclusions

Apatinib was well tolerated after R0 resection for HCC with PVTT. The median RFS in this group was improved compared with previous reports. However, further, larger sample size trials, which will include a control group, should be performed to confirm these findings. Based on this study and another study carried out in our hospital (adjuvant therapy with apatinib plus SHR1210, clinicaltrial.gov identifier NCT03722875), a phase III randomized placebo-controlled clinical trial evaluating apatinib plus SHR1210 as adjuvant therapy is in plan.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-6181

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-6181

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-6181). HCS reports personal fees from Bayer, personal fees from Eisai, personal fees from MSD, personal fees from Hengrui Co., Ltd., personal fees from Innovent Biologics, outside the submitted work; XDZ reports personal fees from Eisai, personal fees from MSD, personal fees from Hengrui Co. Ltd., outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Zhongshan Hospital (No. B2017-065R) and informed consent was given by all individual participants.

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