Transarterial Chemoembolization Combined with Apatinib for Treatment of Advanced Hepatocellular Carcinoma: Analysis of Survival and Prognostic Factors

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[Abstract] Objective: Apatinib is a novel inhibitor of vascular endothelial growth factor receptor-2. The goal of this study was to evaluate overall survival (OS) after a combination of transarterial chemoembolization (TACE) and apatinib in patients with advanced hepatocellular carcinoma (HCC) and to identify the factors affecting patient survival. Methods: Fifty-one patients with advanced HCC who received TACE in combination with apatinib in our hospital from June 2015 to May 2017 were enrolled. The OS and progression-free survival (PFS) were calculated using the Kaplan-Meier method. The log-rank test and Cox regression model were used to determine the factors affecting OS. Results: The median OS and PFS of the patients were 15 months and 10 months, respectively. The 1-, 2-, and 3-year survival rates were 64.7%, 23.5%, and 1.8%, respectively. Univariate survival analysis showed that patients with Child-Pugh A (P=0.006), reduction rate of proper hepatic artery (P=0.016), hand-foot syndrome (P=0.005), secondary hypertension (P=0.050), and without ascites (P=0.010) had a better OS. Multivariate analysis showed that hand-foot syndrome (P=0.014), secondary hypertension (P=0.017), and reduction rate of proper hepatic artery (P=0.025) were independent predictors of better OS. Conclusion: TACE combined with apatinib is a promising treatment for advanced HCC. Hand-foot syndrome, secondary hypertension, and the reduction rate of proper hepatic artery were associated with a better OS.

Key words: chemoembolization; therapeutic; apatinib; molecular targeted therapy; survival; factor analysis, statistical

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer deaths globally. More than 50% of HCC cases occur in China. Current treatments for HCC include ablation, resection, liver transplantation, transarterial chemoembolization (TACE), systemic therapies, and optimal supportive care[11]. Unfortunately, a considerable number of Chinese patients are in the advanced stage of HCC when initially diagnosed, resulting in a poor prognosis. Sorafenib, an oral multikinase inhibitor that has antiproliferative and antiangiogenic effects, is the standard systemic therapy for advanced HCC, but its long-term efficacy remains unsatisfactory.

Although TACE is recommended for intermediate-stage HCC, surveys have shown that the procedure is widely used to treat advanced-stage liver cancer[2, 3]. TACE, which consists of the intra-arterial infusion of a chemotherapeutic agent followed by embolization of the tumor-feeding arteries, can achieve a substantial cytotoxic and hypoxic/ischemic tumor necrosis[4]. However, there is local hypoxia following TACE that can activate hypoxia-inducible factor-1 (HIF-1) and up-regulate the level of vascular endothelial growth factor (VEGF), thereby promoting tumor angiogenesis and recurrence[5].

The combination of TACE and a systemic therapy that targets angiogenesis may constitute an effective strategy to improve outcomes in patients with advanced HCC. Although a recent phase III trial has shown that sorafenib combined with TACE failed to improve survival in patients with advanced HCC compared with sorafenib alone[6], combination
of TACE with other molecular targeted therapies is worth further investigation. Apatinib is another small-molecule tyrosine kinase inhibitor that exhibits higher selective inhibition of VEGF receptor-2 than sorafenib, which can block the migration and proliferation of vascular endothelial cells, reduce tumor microvessel density, and inhibit tumor growth[17–9]. Recent studies have found that the adjuvant apatinib can enhance the effectiveness of TACE for advanced HCC[10–15]. However, the factors affecting patient survival after the combination treatment are not yet fully understood. This study was designed to evaluate the long-term outcomes of TACE in combination with apatinib for advanced HCC and its predictors.

1 MATERIALS AND METHODS

1.1 Selection of Patients

A retrospective analysis was conducted in consecutive HCC patients who received TACE combined with apatinib at Union Hospital, Tongji Medical College, Huazhong University of Science and Technology from June 2015 to May 2017. The criteria for patient selection included patients aged >18 years with HCC, unresectable tumors with macrovascular invasion and/or extrahepatic spread, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, liver function Child-Pugh Class A and B[16], no previous chemotherapy, ablation, radiotherapy, or coagulation. Patients were also excluded if they had severe dysfunction of kidney, heart, lung, or coagulation. Patients were also excluded if they had hepatic encephalopathy or hepatorenal syndrome, severe dysfunction of kidney, heart, lung, or coagulation. Patients were also excluded if they had discontinued apatinib >1 month or were lost to follow-up.

This study was approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent was obtained from all patients.

1.2 Combination Treatment of TACE and Apatinib

All patients received TACE in combination with apatinib. The TACE procedure was performed under fluoroscopic guidance. The Seldinger technique was used to puncture the femoral artery and a vascular sheath was placed. A 5-F Yashiro or RH catheter was used to catheterize the celiac trunk and superior mesenteric artery. Selective arteriography was performed to detect hypervascular masses. A 2.7-F Terumo Progreat microcatheter was then introduced coaxially through the 5-F catheter into the branches that supply the tumor. A mixture of single (epirubicin 40–60 mg) or multiple chemotherapeutic agents (epirubicin 40–60 mg, oxaliplatin 50 mg and raltitrexed 2–4 mg) with 5–20 mL of lipiodol was delivered and additional gelatin sponge particles 350–560 μm in size were injected to block the tumor-feeding arteries. The embolization endpoint was complete stasis or near stasis of the blood flow. In cases of bilobar or massive lesions, at least two TACE procedures were performed.

Apatinib was initiated at an oral dose of 500 mg/day during 3–5 days after TACE. The dose reduction of apatinib was based on the patient’s tolerance to the drug. Adverse events were monitored and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. If the adverse events of apatinib were equal to or greater than grade 3, the dose of apatinib was reduced to 250 mg/day to relieve or eliminate the adverse events. If the adverse events (≥ grade 3) continued after the dose adjustment or apatinib-related gastrointestinal hemorrhage occurred, the apatinib treatment was discontinued. For patients who required multiple TACE procedures, the apatinib was withdrawn 2 days before TACE and resumed 3–5 days after TACE.

1.3 Follow-Up and Survival Assessment

Patients were followed up at 1 month after TACE, and then every 2–3 months thereafter. Computed topography (CT) scans (non-contrast, arterial, and portal venous phases) and laboratory data were used during these visits for surveillance. Evidence of progressive disease followed the modified Response Evaluation Criteria in Solid Tumors. The endpoints of follow-up were death, loss to follow-up, or the end of the study.

The primary endpoint of this study was overall survival (OS), defined as the time from initiation of the combination treatment to death. Patients who remained alive at the end of follow-up were censored. The secondary endpoint was progression-free survival (PFS), defined as the time from the treatment initiation to either radiological progression or death.

To identify factors that might predict survival, the following variables were analyzed: hepatitis B virus (HBV), ECOG score, Child-Pugh grade, alpha fetoprotein (AFP), number of lesions, size of dominant lesion, macrovascular invasion, extrahepatic spread, ascites, number of TACE procedures, changes in the proper hepatic artery, hand-foot syndrome, secondary hypertension, diarrhea, and proteinuria. The reduction rate of proper hepatic artery was defined as a percentage of the difference in the vessel diameter between the baseline and the first follow-up DSA images (1–3 months). The median change in the proper hepatic artery of 51 patients was used as the cut-off value, which converted the degree of the vessel change into mild (≤ median) and severe (> median).

1.4 Statistical Analysis

Survival times and survival rates were calculated using the Kaplan-Meier method. A paired t test was
used to compare the difference in the common hepatic artery diameter before and after combination treatment. For OS, the log-rank test and life-table method were used for the univariate analysis. Any predictors that were significant at $P<0.05$ in the univariate analysis were candidates for entry into a Cox regression model for the multivariate analysis. Statistical analysis was performed using SPSS 17.0 (SPSS Inc., USA). A $P<0.05$ was considered to indicate a significant difference.

2 RESULTS

2.1 Patient Characteristics

A total of 98 HCC patients received TACE combined with apatinib in our hospital between June 2015 and May 2017. Eighteen patients were excluded due to apatinib discontinuation, and 29 patients were lost to follow-up. Finally, 51 patients were included in this study. The overall patient characteristics are shown in table 1. This cohort consisted of 44 males and 7 females. The mean age was 47.9±10.1 years (mean±standard deviation). Patients presented with an average of 2.8±1.8 lesions (range, 1–8 lesions). The largest diameter of tumor size measured 9.3±5.0 cm (range, 1.2–19.1 cm) (table 1).

2.2 Treatment Process

TACE was successfully performed in patients (fig. 1). Of the 51 patients, 11 received 1 TACE session, 10 received 2 sessions, and 30 received 3 or more sessions after inclusion. The median number of TACE treatments per patient was 3.6±2.8 (range, 1–14).

As for the administration of apatinib, 500 mg per day was given in 45 patients, whereas the dose was reduced to 250 mg per day in the other 6 patients due to the development of grade 3 adverse reactions. The most common grade 3 adverse reactions occurred in 9.8% of patients (5/51 patients), which included hand-foot syndrome, secondary hypertension, diarrhea, and proteinuria during the entire period of combination treatment (table 1).

2.3 Survival and Prognostic Factors

The median follow-up time was 15 months (range, 3–38 months). Forty-four (86.3%) of the 51 patients died and 7 (13.7%) remained alive during the follow-up period (June 2015 to May 2019). The median OS was 15 months (range, 3–38 months) (fig. 2A), and the median PFS was 10 months (range, 1–24 months) (fig. 2B). The cumulative OS rates at 1, 2, and 3 years were 64.7%, 23.5%, and 1.8%, respectively.

In the univariate analysis, patients with Child-Pugh grade A had a significantly longer median OS than Child-Pugh grade B patients (17 months vs. 10 months, $P=0.006$) (fig. 3A). Patients without ascites had a significantly longer median OS than those with ascites (17 months vs. 9 months, $P=0.010$) (fig. 3B).

![A representative patient undergoing TACE combined with apatinib](attachment:image)

**Fig. 1** A representative patient undergoing TACE combined with apatinib

A: Contrast-enhanced CT image before TACE showed a hypervascular mass (arrow) in the segment IV, V, and VIII. B: Hepatic arteriogram during the first TACE demonstrated the hypervascular mass, which supplied with branches of the right (arrowhead) and middle hepatic (arrow) and the gastroduodenal (asterisk) artery. C: Arteriogram after chemoembolization confirmed occlusion of the tumor-feeding arteries. Apatinib was initiated 3 days after the first TACE. D: Contrast-enhanced CT image 6 months after the combination treatment demonstrated lipiodol deposition in the treated lesion (arrow) with decreased tumor size.

| Table 1 Patient characteristics and univariate analysis for OS |
|-------------------|-------------------|-------------------|-------------------|
| Variable          | Number of patients | Median OS (month) | $P$ value |
| HBV               |                   |                   | 0.447          |
| Negative          | 4 (7.8%)          | 10                |               |
| Positive          | 47 (92.2%)        | 15                |               |
| ECOG score        |                   |                   | 0.373          |
| 0                 | 0 (0)             |                   |               |
| 1                 | 42 (82.4%)        | 15                |               |
| 2                 | 9 (17.6%)         | 15                |               |
| Child-Pugh grade  |                   |                   | 0.006          |
| A                 | 44 (86.3%)        | 17                |               |
| B                 | 7 (13.7%)         | 10                |               |
| AFP (μg/L)        |                   |                   | 0.076          |
| <400              | 23 (45.1%)        | 19                |               |
| ≥400              | 28 (54.9%)        | 12                |               |
| Number of lesions |                   |                   | 0.666          |
| 1                 | 17 (33.3%)        | 15                |               |
| ≥2                | 34 (66.7%)        | 15                |               |
| Size of dominant lesion |               |                   | 0.647          |
| <5 cm             | 12 (23.5%)        | 18                |               |
| 5–10 cm           | 18 (35.3%)        | 17                |               |
| >10 cm            | 21 (41.2%)        | 14                |               |
| Macrovacular invasion |               |                   | 0.363          |
| None              | 26 (51.0%)        | 15                |               |
| Portal vein       | 22 (43.1%)        | 13                |               |
| HV and/or IVC     | 3 (5.9%)          | 19                |               |

(Continued to the next page)
The median OS of patients without hand-foot syndrome was 10 months, whereas the median OS of patients with grade 1, 2, and 3 hand-foot syndrome was 14, 21, and 17 months, respectively. Patients with grade 2 hand-foot syndrome had a significantly longer median OS than patients without hand-foot syndrome (21 months vs. 10 months, \(P=0.005\)) (fig. 3C). The median OS of patients without secondary hypertension was 15 months, whereas that of patients with grade 1, 2, and 3 secondary hypertension was 18, 15, and 28 months, respectively. Patients with grade 3 hypertension had a significantly longer median OS than non-hypertensive patients (28 months vs. 15 months, \(P=0.050\)) (fig. 3D).

The diameter of the proper hepatic artery before and after combination therapy was 3.79±1.81 mm and 3.40±1.66 mm, respectively, with a statistically significant difference (\(P<0.001\)). The median reduction rate of the proper hepatic artery after treatment was 7.7%. Patients with a mildly reduced diameter of the proper hepatic artery had a longer median OS than those with severely reduced vessel diameters (23 months vs. 13 months, \(P=0.016\)) (fig. 3E and table 1).

In the multivariate analysis, hand-foot syndrome (\(P=0.014\), hazard ratio (HR)=0.634), secondary hypertension (\(P=0.017\), HR=0.606), and the reduction rate of the proper hepatic artery (\(P=0.025\), HR=2.122) were independent predictors of better OS (table 2).

### TABLE 1

| Variable                  | Number of patients | Median OS (month) | \(P\) value |
|---------------------------|--------------------|-------------------|-------------|
| Extrahepatic spread       |                    |                   | 0.285       |
| None                      | 18 (35.3%)         | 14                |             |
| Lymph node                | 11 (21.6%)         | 15                |             |
| Peritoneum                | 9 (17.6%)          | 18                |             |
| Organ metastasis          | 13 (25.5%)         | 12                |             |
| Ascites                   |                    |                   | 0.010       |
| Absent                    | 43 (84.3%)         | 17                |             |
| Present                   | 8 (15.7%)          | 9                 |             |
| Number of TACE            |                    |                   | 0.446       |
| 1                         | 31 (60.7%)         | 15                |             |
| ≥2                        | 20 (39.3%)         | 17                |             |
| Proper hepatic artery     |                    |                   | 0.016       |
| Mild reduction            | 25 (49.0%)         | 23                |             |
| Severe reduction          | 26 (51.0%)         | 12                |             |
| Hand-foot syndrome        |                    |                   | 0.005       |
| None                      | 13 (25.5%)         | 10                |             |
| Grade 1                   | 11 (21.6%)         | 14                |             |
| Grade 2                   | 24 (47.1%)         | 21                |             |
| Grade 3                   | 3 (5.9%)           | 17                |             |
| Secondary hypertension    |                    |                   | 0.050       |
| None                      | 22 (43.1%)         | 15                |             |
| Grade 1                   | 18 (35.3%)         | 18                |             |
| Grade 2                   | 9 (17.6%)          | 16                |             |
| Grade 3                   | 2 (3.9%)           | 28                |             |
| Diarrhea                  |                    |                   | 0.102       |
| None                      | 40 (78.4%)         | 14                |             |
| Grade 1                   | 7 (13.7%)          | 18                |             |
| Grade 2                   | 4 (7.8%)           | 15                |             |
| Proteinuria               |                    |                   | 0.373       |
| None                      | 29 (56.9%)         | 14                |             |
| Grade 1                   | 6 (11.8%)          | 15                |             |
| Grade 2                   | 16 (31.3%)         | 19                |             |

HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; AFP, alpha fetoprotein; HV, hepatic vein; IVC, inferior vena cava; TACE, transarterial chemoembolization; OS, overall survival

The median OS of patients without hand-foot syndrome was 10 months, whereas the median OS of patients with grade 1, 2, and 3 hand-foot syndrome was 14, 21, and 17 months, respectively. Patients with grade 2 hand-foot syndrome had a significantly longer median OS than patients without hand-foot syndrome (21 months vs. 10 months, \(P=0.005\)) (fig. 3C). The median OS of patients without secondary hypertension was 15 months, whereas that of patients with grade 1, 2, and 3 secondary hypertension was 18, 15, and 28 months, respectively. Patients with grade 3 hypertension had a significantly longer median OS than non-hypertensive patients (28 months vs. 15 months, \(P=0.050\)) (fig. 3D). The diameter of the proper hepatic artery before and after combination therapy was 3.79±1.81 mm and 3.40±1.66 mm, respectively, with a statistically significant difference (\(P<0.001\)). The median reduction rate of the proper hepatic artery after treatment was 7.7%. Patients with a mildly reduced diameter of the proper hepatic artery had a longer median OS than those with severely reduced vessel diameters (23 months vs. 13 months, \(P=0.016\)) (fig. 3E and table 1).

In the multivariate analysis, hand-foot syndrome (\(P=0.014\), hazard ratio (HR)=0.634), secondary hypertension (\(P=0.017\), HR=0.606), and the reduction rate of the proper hepatic artery (\(P=0.025\), HR=2.122) were independent predictors of better OS (table 2).

### DISCUSSION

According to BCLC staging and treatment criteria, systemic therapies are the standard treatment for this stage of HCC, and the median OS was reported to be 6.5–11.8 months after treatment with sorafenib\[^16^\]. However, based on the Chinese primary liver cancer diagnosis and treatment guidelines, HCC patients with vascular invasion and/or extrahepatic metastasis are recommended to receive TACE treatment, systemic therapy, surgical resection, radiotherapy, or combination therapy\[^17^\]. Apatinib is a novel vascular endothelial growth factor receptor 2 kinase inhibitor that has been reported to be effective against a variety of solid tumors\[^18^\]. In a recent phase III randomized controlled trial, apatinib has shown survival benefits compared to placebo in Chinese patients with advanced HCC who failed or were intolerant to the first-line systemic therapy\[^19^\]. In this study, we demonstrated that TACE combined with apatinib achieved a median
OS of up to 15 months and that hand-foot syndrome, secondary hypertension, and reduction rate of proper hepatic artery were independent predictors of better OS.

Although the efficacy of sorafenib combined with TACE in the treatment of advanced HCC is debatable, the combination of apatinib with TACE may provide a new treatment strategy. Two retrospective studies compared sorafenib combined with TACE versus sorafenib alone for advanced HCC and found that the combination therapy improved patient survival\[^{10, 20, 21}\]. However, a recent phase III clinical trial showed that the addition of TACE to sorafenib failed to achieve significant survival benefit, although it significantly improved PFS, time to progression, and tumor response\[^{6}\]. The reported median OS and PFS in sorafenib plus TACE group were 12.8–17.3 months\[^{6, 20–22}\] and 5.2–5.4 months\[^{6, 22}\], respectively. In contrast, previous studies\[^{23, 24}\] suggested that TACE combined with apatinib represented an effective combination therapy for the treatment of advanced HCC and had a certain degree of safety. For the combination of apatinib and TACE compared with TACE alone, the median OS and PFS of the combination treatment group were reported to be 11.9–22 months\[^{10, 25–27, 14}\] and 4.5–9.5 months\[^{10, 26}\], respectively. Our study showed that the median OS and PFS of 51 patients with advanced HCC were 15 and 10 months, respectively. It should be noted that the OS and PFS in this study were based on the time of initiation of the combination treatment, not on the time of diagnosis of advanced HCC. These data suggest that the combination of apatinib with TACE may represent a promising combination therapy for advanced HCC.

There are no established reliable biomarkers to predict the efficacy of systemic therapy with or without TACE for HCC to date. Several previous studies evaluated possible factors affecting survival but yielded conflicting results. Yang et al\[^{10}\] used apatinib combined with TACE to treat advanced HCC and found that patient survival was not associated with any apatinib-related adverse events but with macrovascular invasion and extrahepatic metastases. In contrast, Liao et al\[^{28}\] treated stage IV sarcoma with apatinib and found that post-treatment hypertension, hand-foot syndrome, and proteinuria indicated a favorable prognosis.

### Table 2 Multivariate analysis for overall survival

| Parameter                                  | Hazard ratio | 95% CI      | P-value |
|--------------------------------------------|--------------|-------------|---------|
| Child-Pugh grade                           | 1.092        | 0.388–3.070 | 0.868   |
| Ascites                                    | 2.413        | 0.943–6.173 | 0.066   |
| The reduction rate of proper hepatic artery | 2.122        | 1.100–4.096 | 0.025   |
| Hand-foot syndrome                         | 0.634        | 0.440–0.913 | 0.014   |
| Secondary hypertension                     | 0.606        | 0.402–0.914 | 0.017   |

Fig. 3 Kaplan-Meier survival curves based on Child-Pugh grade (A), ascites (B), hand-foot syndrome (C), secondary hypertension (D), and the proper hepatic artery reduction (E)
adverse events, including hand-foot syndrome and secondary hypertension, may represent independent predictors for patient survival. These adverse events are probably related to the antiangiogenic effect of apatinib resulting in inhibition of VEGF receptor 2. Hand-foot syndrome has been associated with some antineoplastic agents, especially 5-fluoruracil (5-FU) and its derivatives, but the pathogenesis is not understood[29]. As for secondary hypertension, antagonism of VEGF receptor 2, the major endothelial cell receptor in VEGF signaling, decreases nitric oxide (NO) production through numerous downstream pathways. The resultant vasoconstriction may underlie much of the hypertension that results from the use of VEGF inhibitors[30].

A surprising finding was that patients with mildly reduced proper hepatic artery diameter after combination therapy had longer OS than those with severely reduced diameters, which seems to contradict the anti-angiogenic effect of apatinib. In a previous phase II trial, Siegel et al.[31] evaluated the efficacy of bevacizumab, an anti-VEGF monoclonal antibody, in unresectable HCC and found that the mean tumor enhancement was significantly decreased after bevacizumab treatment compared with baseline on contrast-enhanced MR imaging, which was positively correlated with reduction in tumor diameter. The present study employed the change of hepatic artery diameter instead of tumor enhancement as the intratumoral necrosis and lipiodol deposition after TACE impaired the results of measuring tumor enhancement on CT. After the combination therapy, the diameter of the hepatic artery was significantly decreased from 3.79±1.81 mm to 3.40±1.66 mm, which can probably be explained by the antiangiogenic effect of apatinib and the hepatic arterial damage caused by TACE. However, our results showed that the degree of the proper hepatic artery reduction after combination therapy was negatively correlated with OS. This finding may be due to the hepatic artery reduction-related impairment of efficacy of TACE. It is well known that TACE involves the injection of chemotherapy and embolic particles into the tumor-feeding artery via an intraarterially inserted catheter. The more the hepatic artery reduced, the fewer chemotherapeutics and embolic agents are inserted catheter. The more the hepatic artery reduced, the fewer chemotherapeutics and embolic agents are delivered to the tumor via the artery. In this sense, mild reduction in the hepatic artery could represent an optimal anti-angiogenesis effect with the combination therapy of HCC, which reduced the blood supply of the tumor without compromising the effectiveness of TACE. These findings should be confirmed by further studies.

One of the major limitations of this study was that this was a retrospective study, which was inevitably subject to biases. In addition, we did not perform functional imaging targeting tumor vascularization, such as MR perfusion imaging, which limited the evaluation of tumor vascularization. Finally, the sample size of our study was relatively small. Additional prospective randomized trials with larger sample sizes are needed to validate our findings.

In conclusion, TACE combined with apatinib may represent an effective combination therapy for advanced HCC. Hand-foot syndrome, secondary hypertension, and the reduction rate of proper hepatic artery were associated with OS.

Conflict of Interest Statement
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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