Transarterial chemoembolization (TACE) combined with apatinib versus TACE combined with sorafenib in advanced hepatocellular carcinoma patients: a multicenter retrospective study

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Background: The combination of transarterial chemoembolization (TACE) with sorafenib has demonstrated superior efficacy over sorafenib and TACE monotherapy in hepatocellular carcinoma (HCC). Apatinib, a new targeted agent, has been recently reported to prolong the survival of HCC patients, either alone or in combination with TACE. However, the superior regimen between TACE-apatinib and TACE-sorafenib in HCC patients has not been determined. In this study, we compared the efficacy and safety of TACE-apatinib versus TACE-sorafenib in advanced stage HCC patients.

Methods: The data of 201 HCC patients who had received TACE-sorafenib or TACE-apatinib between January 2016 and June 2018 in three hospitals were retrospectively reviewed. Overall survival (OS), progression-free survival (PFS), and adverse effects (AEs) between the two treatment groups were compared. A subgroup analysis based on the doses of targeted agents was also performed.

Results: No significant differences in baseline clinicopathological features were found between the two groups except for dose reduction. The TACE-apatinib group had higher incidences of hypertension, oral or anal ulcer and proteinuria, while the TACE-sorafenib group had higher incidences of diarrhea and alopecia. Grade 3/4 AEs occurred more frequently in the TACE-apatinib group than in the TACE-sorafenib group (52.3% vs. 22.6%, P<0.001). The TACE-sorafenib group had better PFS than the TACE-apatinib group (median PFS: 5.0 vs. 6.0 months, P<0.002) while the two groups showed no difference in OS (median OS: 13.0 vs. 13.0 months, P=0.448). The TACE-apatinib group had a higher rate of targeted agent dose reduction than the TACE-sorafenib group (53.5% vs. 17.4%, P<0.001). When the patients were stratified into normal and reduced-dose subgroups, those who received TACE-sorafenib exhibited improved PFS but similar OS compared with the patients who received TACE-apatinib in the reduced-dose subgroup (median OS: 12.0

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Introduction

In the past decade, the incidence of hepatocellular carcinoma (HCC) has increased despite a downward trend in the incidence of all tumors, and the East Asian region accounts for a substantial portion of new cases (1,2). More than 60% of HCC cases are diagnosed at an intermediate or advanced stage, mostly not amenable for curative therapies (3). Based on the clinical guideline of the European Association for the Study of the Liver, systemic therapy is the current recommended treatment for advanced HCC [Barcelona Clinic Liver Cancer (BCLC) stage C] (4). Sorafenib, a multi-kinase inhibitor that blocks tumor angiogenesis and growth, is recognized as the first targeted agent for advanced HCC. However, sorafenib has demonstrated modest efficacy by prolonging the median overall survival (OS) of HCC patients by 2.8 months compared with placebo (5). In the Asia-Pacific region, this survival benefit was even more marginal (OS: 6.5 vs. 4.2 months) (6). Subsequently, a combination of transarterial chemoembolization (TACE) with sorafenib is recommended to exert a synergistic therapeutic effect in unresectable HCC. The underlying rationale is that sorafenib could inhibit neo-angiogenesis after TACE (7,8). Several trials have demonstrated the feasibility and superior efficacy of this combination therapy in HCC patients compared to sorafenib or TACE monotherapy (9-11). However, unsatisfactory response rate and heterogeneous survival benefits still motivate researchers to seek for new targeted agents, improved interventional therapies and optimal combinations (12-16).

Apatinib is a novel tyrosine kinase inhibitor (TKI) with strong selectivity to vascular endothelial growth factor receptor (VEGFR)-2 (17). In 2014, a phase II clinical study reported that apatinib monotherapy could prolong the OS of advanced HCC patients (18). Considering its potential inhibitory role in post-TACE neo-angiogenesis, a series of studies have shown clinical benefits of TACE-apatinib in unresectable HCC compared with TACE-alone (19-24). However, no previous comparison between TACE-apatinib and TACE-sorafenib has been conducted.

We herein compared the efficacy and safety of TACE-apatinib treatment versus TACE-sorafenib treatment in advanced HCC patients. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5360).

Methods

Study design

This retrospective study included patients from three academic hospitals in China (the Sun Yat-sen University Cancer Center, the Third Affiliated Hospital of Sun Yat-sen University, and the Second Affiliated Hospital of Guangzhou Medical University) between January 2016 and June 2018. This study was approved by the ethics committees of all three hospitals (No. R2019-153) in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013). Written informed consent was not required due to the retrospective nature of this study.

Inclusion criteria for this study were the following: (I) age between 18–75 years; (II) stage C according to the BCLC staging system; (III) Child-Pugh (CP) Class A or B liver function; and (IV) a score of 0 or 1 according to the Eastern Cooperative Group performance status. The exclusion criteria were as follows: (I) heart, lung, or kidney dysfunction; (II) inadequate bone marrow function (white blood cell count <3.0×10^9/L, platelet count <40×10^9/L, or absolute neutrophil count <1.5×10^9/L); (III) other primary...
malignancies or immune deficiencies; (IV) concomitant antineoplastic treatments except TACE, sorafenib, or apatinib before disease progression in this study; (V) concomitant administration of sorafenib and apatinib or switching to the opposite treatment before disease progression in this study; and (VI) an interval over 15 days between TACE and the administration of targeted agents. All patients in this study had been informed of choices of targeted agents and they made their decisions based on the full communication between patients and doctors as well as their personal willingness. Accordingly, the patients were classified into two groups, namely the TACE-sorafenib and the TACE-apatinib group.

**Therapeutic method**

**TACE**

TACE was performed by experienced radiologists in the three hospitals using similar protocols. After intubation, the angiography of hepatic and related vessels was performed to evaluate the blood supply to the liver and the feasibility of TACE. Once the catheterization of tumor-feeding arteries was completed, chemotherapeutic agents were mixed and infused via a catheter inserted into the arteries. The infusion emulsion contained 30–50 mg of epirubicin (Pharmorubicin; Pfizer, Jiangsu, China), 30–50 mg of lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd., Hainan, China), and 5–15 mL of lipiodol (Lipiodol Ultrafluide; France). Absorbable gelatin sponge particles (Gelfoam; Hangzhou alc Ltd., Zhejiang, China) were subsequently used to embolize the arteries. Response to TACE was evaluated 1 month after the operation via contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). Repeated TACE was recommended if shrinkage of lipiodol deposition, recurrence of residual lesions, or intrahepatic progression was observed on follow-up imaging, using a similar treatment protocol as the initial operation.

**Administration of targeted agents**

The administration was performed within 15 days after first TACE operation and continued until intolerable adverse events (AEs) occurred or disease progression developed. Initially, 500 mg of daily apatinib (Hengrui Pharmaceutical Co., Ltd., Shanghai, China) and 400 mg of sorafenib (Bayer Health-care, Leverkusen, Germany) twice daily were prescribed, respectively. If the patients could not tolerate the initial dose, stepwise dose modification was recommended as follows: from 250 mg daily to 250 mg every other day for apatinib, and from 600 mg daily to 400 mg daily, then to 400 mg every other day for sorafenib (21,25). Re-escalation to the last-step dose was advised once the AEs were alleviated or the patients could tolerate them.

**Follow-up, endpoints, and evaluation of therapeutic effect**

The patients were regularly followed up and examined using abdominal contrast-enhanced CT or MRI every 4–6 weeks during follow-up periods. OS and progression-free survival (PFS) were compared between the two groups. OS was defined as the interval between the date of first treatment and the date of death or last follow-up (October 1, 2019). PFS was defined as the interval between the date of first treatment and the date of disease progression, death, or last follow-up. According to the modified response evaluation criteria in solid tumor, the patients’ imaging examination results were evaluated by at least two radiologists with 10 years of experience, using the following 4 levels of treatment responses: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) (26). Referring to a previous study, disease control rate (DCR) was defined as the proportion of patients who maintained a tumor response of CR, PR, or SD for at least 12 weeks from first manifestation (27). AEs were recorded and graded according to the Common Terminology Criteria for Adverse Events (version 4.0).

**Statistics analysis**

Analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and R 3.6.0 software (R Foundation for Statistical Computing, Vienna, Austria). Unless indicated otherwise, comparison was conducted using the chi-square test for categorical variables and the t-test for continuous variables. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. The prognostic value of potential predictors was assessed using the Cox proportional hazard regression model. Only variables with P value <0.10 in univariable analysis were added in multivariable analysis for identifying independent prognostics factors affecting OS or PFS. Inspection level was set at α=0.05.

**Results**

**Baseline characteristics**

Between January 2016 and June 2018, a total of 201 HCC
patients who had undergone TACE-apatinib (n=86) or TACE-sorafenib (n=115) treatment in the three hospitals were evaluated (Figure 1). The median age of these patients was 52 (range, 23–75) years. The baseline characteristics of the two groups are listed and compared in Table 1. All patients were diagnosed with BCLC stage C HCC and 116 of them had distant metastasis while 126 had major vascular invasion. Differences in the characteristics were not significant between the two groups except for dose reduction. Particularly, the rate of dose reduction was higher in the TACE-apatinib group than in the TACE-sorafenib group (53.5% vs. 17.4%, P<0.001).

**AEs and safety assessment**

Treatment-related AEs are listed in Table 2. Hand-foot syndrome was the most common AE with similar incidences in both groups (TACE-apatinib: 58.1%; TACE-sorafenib: 51.3%; P=0.336). Other common AEs in the TACE-apatinib group were hypertension (39.5%), proteinuria (37.2%), and oral or anal ulcer (32.6%). In the TACE-sorafenib group, patients also suffered from diarrhea (31.3%), fever (30.4%), and abdominal pain (26.1%). In comparison, the TACE-apatinib group had higher incidences of hypertension, oral or anal ulcer and proteinuria while the TACE-sorafenib group had higher incidences of diarrhea and alopecia (all P<0.05). These AEs were predominantly related to the targeted agents, while TACE-related AEs such as fever, abdominal pain, and pleural effusion were comparable in the two groups. Moreover, the TACE-apatinib group had a higher incidence of severe (grade 3/4) AEs than the TACE-sorafenib group (52.3% vs. 22.6%, P<0.001). Only one patient developed TACE-related severe AEs, but the TACE protocol was not affected.

Overall, 66 of the 201 patients had permanently reduced the doses or discontinued the drug administration due to the AEs before disease progression (TACE-apatinib, n=46; TACE-sorafenib, n=20). After dose reduction and symptomatic treatments, their symptoms gradually receded. The rest of the patients developed tolerable AEs and eventually resumed the initial dose. No hepatic failure, unexpected AEs, or grade 5 AEs were observed.

**Survival analysis**

During the follow-up, 134 of the 201 patients died from HBV...
| Characteristics                | TACE-sorafenib group (n=115) | TACE-apatinib group (n=86) | P     |
|-------------------------------|------------------------------|---------------------------|-------|
| Sex                           |                              |                           | 0.950 |
| Men                           | 104 (90.4)                   | 78 (90.7)                 |       |
| Women                         | 11 (9.6)                     | 8 (9.3)                   |       |
| Age (years)                   |                              |                           | 0.699 |
| <52                           | 53 (46.1)                    | 42 (48.8)                 |       |
| ≥52                           | 62 (53.9)                    | 44 (51.2)                 |       |
| AFP (ng/mL)                   |                              |                           | 0.528 |
| <400                          | 51 (44.3)                    | 42 (48.8)                 |       |
| ≥400                          | 64 (55.7)                    | 44 (51.2)                 |       |
| HBV status                    |                              |                           | 0.237 |
| Positive                      | 105 (91.3)                   | 74 (86.0)                 |       |
| Negative                      | 10 (8.7)                     | 12 (14.0)                 |       |
| Child-Pugh                    |                              |                           | 0.700 |
| Class A                       | 96 (83.5)                    | 70 (81.4)                 |       |
| Class B                       | 19 (16.5)                    | 16 (18.6)                 |       |
| Tumor size (cm)               |                              |                           | 0.190 |
| <5                            | 34 (29.6)                    | 33 (38.4)                 |       |
| ≥5                            | 81 (70.4)                    | 53 (61.6)                 |       |
| Tumor number                  |                              |                           | 0.313 |
| Single                        | 35 (30.4)                    | 32 (37.2)                 |       |
| Multiple                      | 80 (69.6)                    | 54 (62.8)                 |       |
| Vascular invasion             |                              |                           | 0.748 |
| Present                       | 71 (61.7)                    | 55 (64.0)                 |       |
| Absent                        | 44 (38.3)                    | 31 (36.0)                 |       |
| Distant metastasis            |                              |                           | 0.915 |
| Present                       | 66 (57.4)                    | 50 (58.1)                 |       |
| Absent                        | 49 (42.6)                    | 36 (41.9)                 |       |
| Dose reduction                |                              |                           | <0.001|
| Present                       | 20 (17.4)                    | 46 (53.5)                 |       |
| Absent                        | 95 (82.6)                    | 40 (46.5)                 |       |
| Cycles of TACE                |                              |                           | 0.224 |
| Duration of targeted drugs (months) | 3.5±1.9                     | 3.2±1.7                   |       |
|                               |                              |                           | 0.090 |
|                               |                              |                           |       |

Data are shown as numbers of events with percentages in parentheses or averages ± standard deviations. TACE, transarterial chemoembolization; AFP, alpha fetoprotein; HBV, hepatitis B virus.
tumor progression. No significant difference was observed in OS between the two groups (median OS: 13.0 vs. 13.0 months, P=0.448). However, the TACE-sorafenib group exhibited improved PFS compared with the TACE-apatinib group (median PFS: 5.0 vs. 6.0 months, P=0.002) (Figure 2). In the TACE-apatinib group, 3 patients had PR (3.5%) and 47 patients had SD (54.7%). In the TACE-sorafenib group, 2 patients had CR (1.7%), 30 patients had PR (26.1%), and 50 patients had SD (52.2%). The DCR was 58.1 % and 80.0% in the TACE-apatinib group and the TACE-sorafenib group, respectively (P=0.001).

Considering the higher rate of dose reduction in the TACE-apatinib group, a subgroup analysis based on the treatment dose and their median average daily doses were 432 mg of apatinib or 770 mg of sorafenib. The average daily dose was determined within the patient-based actual days of administration excluding treatment interruption. In the reduced-dose subgroup, TACE-sorafenib conferred a survival benefit in terms of PFS compared with TACE-apatinib but failed in terms of OS (median OS: 12.0 vs. 13.3 months, P=0.614; median PFS: 3.0 vs. 7.0 months, P<0.001). In the normal-dose subgroup, no significant differences in terms of OS and PFS were observed between the two treatment arms (median OS: 14.0 vs. 13.0 months, P=0.710; median PFS: 7.0 vs. 6.0 months, P=0.918), respectively (Figure 3). Furthermore, the normal-dose subgroup had superior PFS but similar OS compared with the reduced-dose subgroup in the TACE-apatinib group (median OS: 14.0 vs. 12.0 months, P=0.827; median PFS: 7.0 vs. 3.0 months, P<0.001). However, in the TACE-sorafenib group, the normal-dose subgroup had no survival benefits in terms of both OS and PFS, compared with the reduced-dose subgroup (median OS: 13.0 vs. 13.3 months, P=0.788;
Figure 2 Kaplan-Meier survival curves. OS (A) and PFS (B) among all patients. HR, hazard ratio; CI, confidence interval; TACE, transarterial chemoembolization; OS, overall survival; PFS, progression-free survival.

Figure 3 Kaplan-Meier survival curves. (A) OS in the reduced-dose subgroup; (B) PFS in the reduced-dose subgroup; (C) OS in the normal-dose subgroup; (D) PFS in the normal-dose subgroup. HR, hazard ratio; CI, confidence interval; TACE, transarterial chemoembolization; OS, overall survival; PFS, progression-free survival.
median PFS: 6.0 vs. 7.0 months, P=0.866) (Figure 4).

**Prognostic factors affecting OS and PFS**

Multivariable analyses confirmed that age ≥52 [hazard ratio (HR): 0.57; 95% confidence interval (CI), 0.40–0.80; P=0.001], CP class B (HR: 1.65; 95% CI, 1.09–2.51; P=0.019), and tumor size ≥5 cm (HR: 1.61; 95% CI, 1.10–2.35; P=0.014) were independent prognostic factors for OS among all patients. In the reduced-dose subgroup, age ≥52 (HR: 0.45; 95% CI, 0.23–0.87, P=0.018) and CP class B (HR: 2.40; 95% CI, 1.22–4.69; P=0.011) were independent prognostic factors for OS. In the normal-dose subgroup, age ≥52 (HR: 0.58; 95% CI, 0.38–0.88, P=0.010) was the only independent prognostic factor for OS (Table 3).

For PFS, multivariable analyses confirmed that age ≥52 (HR: 0.68; 95% CI, 0.51–0.92; P=0.012), tumor size ≥5 cm (HR: 1.44; 95% CI, 1.04–1.99; P=0.026), TACE-apatinib (HR: 1.53; 95% CI, 1.11–2.10; P=0.010), and dose reduction (HR: 1.65; 95% CI, 1.19–2.28; P=0.003) were independent prognostic factors for PFS among all patients. In the reduced-dose subgroup, CP class B (HR: 2.82; 95% CI, 1.49–5.33; P=0.001) and TACE-apatinib (HR: 3.07; 95% CI, 1.59–5.92, P=0.001) were independent prognostic factors for PFS. In the normal-dose subgroup, tumor size ≥5 cm (HR: 1.48; 95% CI, 1.01–2.17; P=0.044) was the only independent prognostic factor for PFS (Table 4).

**Treatments after tumor progression**

After tumor progression had been confirmed by radiological results, 83 of the 201 patients received subsequent
| Covariates                             | All patients (n=201) | Reduced-dose subgroup (n=66) | Normal-dose subgroup (n=135) |
|----------------------------------------|----------------------|-----------------------------|-----------------------------|
|                                        | Numbers              | HR (95% CI)                  | P                           | Numbers              | HR (95% CI)                  | P                           | Numbers              | HR (95% CI)                  | P                           |
| **Univariable analysis**                |                      |                              |                             |                          |                              |                             |                          |                              |                             |
| Sex (men vs. women)                    | 182 vs. 19           | 1.37 (0.74–2.55)             | 0.317                       | 62 vs. 4                | 1.18 (0.28–4.92)             | 0.820                       | 120 vs. 15           | 1.39 (0.70–2.77)             | 0.351                       |
| Age (≥52 vs. <52 years)                | 106 vs. 95           | 0.53 (0.38–0.75)             | <0.001                       | 28 vs. 38               | 0.51 (0.27–0.97)             | 0.039                       | 78 vs. 57            | 0.55 (0.36–0.83)             | 0.005                       |
| AFP level (≥400 vs. <400 ng/mL)        | 108 vs. 93           | 1.33 (0.94–1.88)             | 0.104                       | 31 vs. 35               | 1.30 (0.71–2.38)             | 0.398                       | 77 vs. 58            | 1.42 (0.93–2.16)             | 0.109                       |
| HBV status (positive vs. negative)     | 179 vs. 22           | 1.04 (0.60–1.82)             | 0.880                       | 60 vs. 6                | 1.28 (0.39–4.17)             | 0.684                       | 119 vs. 16           | 0.98 (0.52–1.84)             | 0.938                       |
| Child Pugh Class (B vs. A)             | 35 vs. 166           | 1.78 (1.17–2.69)             | 0.007                       | 14 vs. 52               | 2.53 (1.30–4.91)             | 0.006                       | 21 vs. 114           | 1.41 (0.82–2.43)             | 0.217                       |
| Tumor size (≥5 vs. <5 cm)              | 134 vs. 67           | 1.68 (1.15–2.44)             | 0.007                       | 47 vs. 19               | 2.03 (0.94–4.38)             | 0.072                       | 87 vs. 48            | 1.59 (1.02–2.64)             | 0.041                       |
| Tumor number (multiple vs. single)      | 134 vs. 67           | 0.98 (0.69–1.40)             | 0.909                       | 45 vs. 21               | 0.78 (0.42–1.47)             | 0.448                       | 89 vs. 46            | 1.14 (0.74–1.77)             | 0.555                       |
| Vascular invasion (present vs. absent)  | 126 vs. 75           | 1.24 (0.87–1.78)             | 0.232                       | 43 vs. 23               | 1.44 (0.74–2.82)             | 0.286                       | 83 vs. 52            | 1.17 (0.76–1.79)             | 0.478                       |
| Distant metastasis (present vs. absent) | 116 vs. 85           | 1.14 (0.81–1.61)             | 0.447                       | 39 vs. 27               | 1.35 (0.72–2.53)             | 0.343                       | 77 vs. 58            | 1.09 (0.72–1.65)             | 0.897                       |
| Treatments (TACE-apatinib vs. TACE-sorafenib) | 86 vs. 115        | 1.15 (0.80–1.63)             | 0.455                       | 46 vs. 20               | 1.19 (0.60–2.35)             | 0.622                       | 40 vs. 95            | 1.09 (0.68–1.75)             | 0.714                       |
| Dose reduction (reduced vs. normal)     | 66 vs. 135           | 1.13 (0.78–1.62)             | 0.522                       | –                      | –                            | –                           | –                      | –                            | –                           |
| **Multivariable analysis**             |                      |                              |                             |                          |                              |                             |                          |                              |                             |
| Age (≥52 vs. <52 years)                | 106 vs. 95           | 0.57 (0.40–0.80)             | 0.001                       | 28 vs. 38               | 0.45 (0.23–0.87)             | 0.018                       | 78 vs. 57            | 0.58 (0.38–0.88)             | 0.010                       |
| Child Pugh Class (B vs. A)             | 35 vs. 166           | 1.65 (1.09–2.51)             | 0.019                       | 14 vs. 52               | 2.40 (1.22–4.69)             | 0.011                       | –                      | –                            | –                           |
| Tumor size (≥5 vs. <5 cm)              | 134 vs. 67           | 1.61 (1.10–2.35)             | 0.014                       | –                      | –                            | –                           | –                      | –                            | –                           |

OS, overall survival; HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; HBV, hepatitis B virus; TACE, transarterial chemoembolization.
Table 4 The univariable and multivariable analysis of PFS on all patients and two subgroups

| Covariates                              | All patients (n=201) | Reduced-dose subgroup (n=66) | Normal-dose subgroup (n=135) |
|-----------------------------------------|----------------------|-------------------------------|-----------------------------|
|                                        | Numbers              | HR (95% CI)                   | P                           | Numbers              | HR (95% CI)                   | P                           |
| Univariable analysis                    |                      |                               |                             |                      |                               |                             |
| Sex (men vs. women)                     | 182 vs. 19           | 1.06 (0.64–1.78)              | 0.820                       | 62 vs. 4             | 1.22 (0.38–3.92)              | 0.740                       |
| Age (≥52 vs. <52 years)                 | 106 vs. 95           | 0.65 (0.49–0.88)              | 0.005                       | 28 vs. 38            | 0.61 (0.36–1.04)              | 0.068                       |
| AFP level (≥400 vs. <400 ng/mL)         | 108 vs. 93           | 1.30 (0.96–1.75)              | 0.087                       | 31 vs. 35            | 1.32 (0.79–2.20)              | 0.294                       |
| HBV status (positive vs. negative)      | 179 vs. 22           | 0.92 (0.58–1.47)              | 0.721                       | 60 vs. 6             | 0.85 (0.36–1.98)              | 0.705                       |
| Child Pugh Class (B vs. A)              | 35 vs. 166           | 1.42 (0.97–2.08)              | 0.069                       | 14 vs. 52            | 2.50 (1.34–4.66)              | 0.004                       |
| Tumor size (≥5 vs. <5 cm)               | 134 vs. 67           | 1.38 (1.01–1.89)              | 0.043                       | 47 vs. 19            | 1.13 (0.66–1.96)              | 0.657                       |
| Tumor number (multiple vs. single)      | 134 vs. 67           | 1.20 (0.88–1.64)              | 0.258                       | 45 vs. 21            | 1.00 (0.58–1.73)              | 0.997                       |
| Vascular invasion (present vs. absent)  | 126 vs. 75           | 1.07 (0.79–1.45)              | 0.666                       | 43 vs. 23            | 1.17 (0.68–2.00)              | 0.578                       |
| Distant metastasis (present vs. absent) | 116 vs. 85           | 1.24 (0.92–1.67)              | 0.159                       | 39 vs. 27            | 1.18 (0.70–1.99)              | 0.539                       |
| Treatments (TACE-apatinib vs. TACE-sorafenib) | 86 vs. 115         | 1.57 (1.16–2.12)              | 0.004                       | 46 vs. 20            | 2.83 (1.48–5.43)              | 0.002                       |
| Dose reduction (reduced vs. normal)     | 66 vs. 135           | 1.85 (1.35–2.54)              | <0.001                      | –                   | –                             | –                           |
| Multivariable analysis                  |                      |                               |                             |                      |                               |                             |
| Age (≥52 vs. <52 years)                 | 106 vs. 95           | 0.68 (0.51–0.92)              | 0.012                       | –                   | –                             | –                           |
| AFP level (≥400 vs. <400 ng/mL)         | –                    | –                             | –                           | –                   | –                             | –                           |
| Child Pugh Class (B vs. A)              | –                    | –                             | –                           | 14 vs. 52            | 2.82 (1.49–5.33)              | 0.001                       |
| Tumor size (≥5 vs. <5 cm)               | 134 vs. 67           | 1.44 (1.04–1.99)              | 0.026                       | –                   | –                             | –                           |
| Treatments (TACE-apatinib vs. TACE-sorafenib) | 86 vs. 115         | 1.53 (1.11–2.10)              | 0.010                       | 46 vs. 20            | 3.07 (1.59–5.92)              | 0.001                       |
| Dose reduction (reduced vs. normal)     | 66 vs. 135           | 1.65 (1.19–2.28)              | 0.003                       | –                   | –                             | –                           |

PFS, progression free survival; HR, hazard ratio; CI, confidence interval; AFP, alpha fetoprotein; HBV, hepatitis B virus; TACE, transarterial chemoembolization.
treatments (Table 5). Among all treatments, the rate of receiving ablative therapies (radiofrequency ablation and microwave ablation) was higher in the TACE-apatinib group than in the TACE-sorafenib group. No significant differences were found in other types of subsequent treatments.

**Discussion**

The potential of combining targeted agents with TACE in patients with unresectable HCC has been arousing researchers’ interests. In this multicenter study, we retrospectively compared the efficacy and safety of TACE-apatinib and TACE-sorafenib. Our findings showed that TACE-sorafenib was superior to TACE-apatinib in prolonging the median PFS, but this superiority was not observed in OS. In a subgroup analysis, TACE-sorafenib also demonstrated a superior survival benefit in terms of PFS as compared to TACE-apatinib in the reduced-dose subgroup. However, there were no significant differences in OS and PFS between the two treatment arms in the normal-dose subgroup.

In recent studies, vascular endothelial growth factor has been considered as one of the most important factors associated with hypoxia-induced angiogenesis after TACE (28). However, other cytokines, such as interleukin-6 and tumor necrosis factor-α could also increase after TACE, leading to neo-angiogenesis and tumor growth (29). Distinct from apatinib, sorafenib can inhibit multiple factors involved in the tumor angiogenesis (30). Therefore, the advantage of apatinib in the selectivity of VEGFR-2 might not translate into the superiority of anti-tumor efficacy.

Despite the observed difference in PFS, no significant difference in OS between the two groups was found. We postulate that subsequent treatments after progression could have had some impactful role. As shown in Table 5, a higher proportion of patients received ablative therapies in the TACE-apatinib group than in the TACE-sorafenib group. Generally, ablation is one of the curative therapies for early/very early-stage patients, not recommended for palliative intent (4). However, several studies have reported that debulking intrahepatic tumor burden could improve the prognosis of advanced HCC patients (31-35). Therefore, it is reasonable to hypothesize that more patients receiving ablation in the TACE-apatinib group could have compensated for the inferiority in PFS compared with the TACE-sorafenib group.

Further, we found that neither macrovascular invasion nor distant metastasis was a risk factor of OS, consistent with previous studies (31-33). Unexpectedly, age was a positive prognostic factor of OS and PFS in the entire cohort. In the normal and reduced dose subgroups, elder patients (≥52 years old) also had longer OS. Apart from selection bias, we hypothesize that HCC could behave more aggressively and lead to a poorer prognosis in younger patients. Most importantly, TACE-apatinib treatment and dose reduction were confirmed to be independent risk factors for PFS among all patients. Particularly, the patients in the reduced-dose subgroup obtained a more favorable PFS benefit from the TACE-sorafenib than the patients in the entire cohort (reduced subgroup vs. entire cohort: HR =3.07 vs. 1.53), indicating that the superiority of TACE-

| Treatments                        | TACE-sorafenib group (n=115) | TACE-apatinib group (n=86) | P   |
|-----------------------------------|------------------------------|---------------------------|-----|
| Ablative therapy                  | 14 (12.2)                    | 21 (24.4)                 | 0.024|
| Palliative surgery                | 5 (4.3)                      | 2 (2.3)                   | 0.700|
| Radioactive seed implanting       | 15 (13.0)                    | 18 (20.9)                 | 0.135|
| Radiotherapy                      | 3 (2.6)                      | 1 (1.2)                   | 0.829|
| New target agents                 | 5 (4.3)                      | 8 (9.3)                   | 0.158|
| Sorafenib                         | 0 (0.0)                      | 7 (8.1)                   | 0.006|
| Regorafenib                       | 5 (4.3)                      | 1 (1.2)                   | 0.371|
| Intra-arterial infusion           | 5 (4.3)                      | 6 (7.0)                   | 0.619|
| Immunotherapy                     | 4 (3.5)                      | 4 (4.7)                   | 0.955|

Data are shown as numbers of events with percentages in parentheses. TACE, transarterial chemoembolization.
sorafenib over TACE-apatinib in terms of PFS among all patients might be partly from dose reduction. Thus, dose reduction could attenuate the efficacy of apatinib, and it was attributable to the targeted agent-related AEs in this study.

The incidence of the agent-related AEs in this study is generally consistent with published articles (6,36,37). Here, severe AEs occurred more frequently in the TACE-apatinib group than in the TACE-sorafenib group. This inferior tolerability profile of apatinib might limit its use in clinical practice. If patients cannot tolerate the AEs of apatinib, a better suggestion might be switching to sorafenib rather than reducing the dose and sequential use of these targeted agents might still prolong the patients’ survival. On the other hand, those who can tolerate the AEs and maintain the initial dose of apatinib might obtain equivalent survival benefits to that obtained from sorafenib. At present, the monthly cost of apatinib in China is nearly 30% lower than that of sorafenib. Therefore, it might become an alternative for those who cannot afford sorafenib. In order to reduce the AEs, some researchers suggest prescribing 500 and 250 mg of apatinib alternatively (37), but further studies are warranted. Besides, lenvatinib, a new targeted agent, was proved to be non-inferior to sorafenib in terms of OS in a phase III HCC trial (38). Considering the high objective response rate of lenvatinib (39), comparing the efficacy and safety of TACE-lenvatinib and TACE-sorafenib would be the next stage of our study.

There were several limitations in this study worth mentioning. First, the retrospective nature of this study made it difficult to avoid recall bias. Second, the relatively small sample size of patients in each group and subgroup hindered further stratified analyses. Third, most patients in this study were hepatitis B virus (HBV)-infected (89.1%) and whether our conclusions could be extended to a non-HBV predominant population also needs verification. Finally, a previous study considers that taking sorafenib prior to first TACE could contribute to the normalization of tumor vessels and improve the efficacy of the combination therapy (11). In this present study, the targeted agents were administrated orally on a non-specific date after the first TACE, which might not reveal the maximal efficacy of the combination therapy.

Conclusions

TACE-apatinib achieved shorter PFS than TACE-sorafenib in advanced HCC patients. However, two treatments exhibited comparable OS. Dose reduction was an independent risk factor associated with PFS and might particularly attenuate the efficacy of apatinib. The safety profile of TACE-apatinib was less well-tolerable than that of TACE-sorafenib. Therefore, TACE-sorafenib could be preferable in the clinical management of advanced HCC but TACE-apatinib could be recommended for the HCC patients who could tolerate the apatinib-associated AEs and maintain the initial dose. All these findings need validation in prospective studies.

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Footnote

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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. In this study, the protocol was approved by the research institutes’ committee (No. B2019-153) and was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2013). Written informed consent was not required due to the retrospective nature of this study.

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