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Original Article

Trans-arterial chemoembolization with sorafenib treatment improves long-term overall survival of patients with intermediate hepatocellular carcinoma

Zhen Yao, Weiyuan Hao, Liwen Guo, Hui Zeng, Yutang Chen

Department of Intervention, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang Province, China

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Abstract: Recently published studies concerning the combination of TACE and sorafenib for patients with intermediate HCC [Barcelona Clinic liver cancer stage B (BCLC-B)] have been limited. The current study aimed to compare the therapeutic effects of trans-arterial chemoembolization (TACE) combined with or without sorafenib treatment in BCLC-B HCC patients. Clinical data of 80 BCLC-B HCC patients was retrospectively analyzed. Moreover, 46 patients received TACE + sorafenib treatment, while 34 patients received TACE alone treatment. Overall survival (OS) and adverse effects (AEs) were compared. Baseline data showed no significant differences between the two groups. Short-term efficacy evaluations revealed no significant differences in CR, PR, SD, and OR rates between the two groups. PD rates were significantly higher in the TACE-treated group (P = 0.018). Median OS was significantly longer in the TACE combined with sorafenib treatment (33.0 [95% CI: 29.7-36.2] vs. 22.0 [95% 17.7-26.3] months, long rank test, P < 0.001). Multivariate regression analysis showed that Child-Pugh classification (HR = 5.32, 95% CI: 1.55-18.30, P = 0.008), tumor diameter (HR = 5.84, 95% CI: 1.47-23.11, P = 0.01), and treatment methods (TACE alone or TACE with sorafenib) (HR = 0.19, 95% CI: 0.07-0.47, P < 0.001) were independently associated with OS. Occurrence rates of rashes, hand-foot skin reactions, and hypertension adverse events were higher in the sorafenib with TACE group (all P < 0.05). However, toxic reactions were all within a controllable range. TACE combined with sorafenib treatment provides extended long-term OS for BCLC-B HCC patients. Thus, it may be a better choice for treatment than TACE alone.

Keywords: Hepatocellular carcinoma, trans-arterial chemoembolization, sorafenib, survival

Introduction

Hepatocellular carcinoma (HCC) is the second most common reason for cancer-related deaths in China [1]. More than 80% of patients with HCC are in advanced stages at diagnosis, with no indications for surgical resection [2, 3]. According to Barcelona clinical liver cancer (BCLC) staging criteria, TACE is mainly used for patients with intermediate stage HCC. TACE has been regarded as the standard treatment for unresectable HCC, providing a modest survival benefit for HCC patients with advanced stages. Since HCC always has intracapsular or extracapsular invasion and viable tumor cells remain after TACE, complete necrosis of target tumors has rarely been achieved by TACE alone [4, 5]. The use of TACE intervention has significant advantages in improving the local control rates of tumors in patients with intermediate-stage [Barcelona Clinic liver cancer stage B (BCLC-B)] HCC, prolonging the survival of patients [6, 7]. However, hypoxia caused by TACE has been associated with increased serum VEGF levels in HCC patients. VEGF is the important mediator of tumor angiogenesis, resulting in the formation of new blood vessels and occurrence of tumor invasion and metastasis [8, 9].

Sorafenib is currently the only targeted drug approved by the FDA- and China FDA (CFDA) for liver cancer [10, 11]. Sorafenib is a multi-kinase inhibitor that blocks tumor vascular growth by inhibiting vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR). Thus, it can inhibit tumor cell proliferation by blocking Raf/MEK/

ERK signaling pathways [12]. TACE can concentrate and isolate chemotherapeutic drugs at the tumor site, blocking the blood supply to tumors. This inevitably leads to hypoxia in tumor cells and surrounding tissues after TACE treatment. This, in turn, promotes neovascularization and makes tumors prone to recurrence and metastasis [13, 14]. Regarding mechanisms, the anti-angiogenic effects of sorafenib may reduce VEGFR levels after TACE, achieving complementary effects with TACE in treatment and enhancing therapeutic effects [7].

Previous studies have confirmed that TACE combined with sorafenib treatment can significantly improve median overall survival (mOS) or time to progression (TTP) in patients with unresectable liver cancer [15, 16]. Currently, multimodal approaches are recommended for treatment of patients with unresectable HCC, either as first-line or subsequent therapy. Recently published studies have focused on the combination of TACE and sorafenib for patients with intermediate HCC (BCLC-B HCC). Therefore, the purpose of the present study was to retrospectively evaluate and compare the benefits of combination treatment of sorafenib and TACE vs. traditional TACE in BCLC-B HCC patients.

Materials and methods

Patients

This study was approved by the Institutional Review Board of Zhejiang Cancer Hospital. The need for individual consent was waived by the committee because of the retrospective nature of the study. This single-center retrospective study collected clinical data of patients diagnosed as intermediate HCC (BCLC-B HCC) at the time of initial diagnosis. They were treated with sorafenib plus TACE or TACE alone, between January 2009 and December 2014, at the Department of Intervention, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China.

Inclusion criteria: 1) 18-75 years old; 2) HCC staged as unresectable BCLC stage B classification; 3) Underwent TACE with sorafenib or TACE alone treatment; 4) Liver function classified as Child-Pugh class A or B, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0; and 5) At least one target lesion could be measured according to the modified Response Evaluation Criteria in Solid Tumors Group (mRECIST) guidelines [17]. Exclusion criteria: 1) Patients that received other therapies, such as hepatectomy, systemic chemotherapy, or radiotherapy procedures; 2) Malignant tumors of other organ systems; 3) HCC of Child-Pugh class C; 4) Any TACE contraindications (e.g., complete obstruction of the portal vein) or sorafenib contraindications (e.g., allergy to sorafenib); and 5) Pregnant or lactating women.

Prior to initial treatment, patients were fully informed of the specific implications of TACE-sorafenib and TACE alone therapies, as well as possible adverse effects (AEs). The fact that there is limited evidence concerning treatment effects was emphasized. The patients received the treatment method they selected. Patients treated with a combination of TACE and sorafenib were classified as the TACE + sorafenib group, while patients that received TACE treatment were classified as the TACE alone group.

Clinical data collection

The following information was extracted from medical records from all patients by two authors, independently (Zhen Yao and Yutang Chen): Age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), Child-Pugh classification, diameter of the tumor, TACE times, and results of serum laboratory tests (Total bilirubin, TBil; Albumin, ALB; Alanine aminotransferase, ALT; Platelet count, PLT; Prothrombin time, PT; α-fetoprotein level, AFP; Lactate dehydrogenase concentrations, LDH).

TACE procedure

All TACE treatments were performed by radiologists with at least 5 years of experience, using conventional technology [18]. A microcatheter was super-selectively inserted into the feeding arteries of tumors, aiming to preserve the liver parenchyma as much as possible. A solution containing chemotherapy drugs (100-150 mg oxaliplatin combined with 0.75-1.0 g fluorouracil) in iodized oil was infused into the arteries. Iodized oil, an embolic agent applied as the drug carrier, allowed the chemotherapy drugs to have affinity for the tumors. It induced the chemotherapeutic drugs into carcinoma tissues, taking the lasting effects on embolization

chemotherapy [19]. TACE was repeated every month if target lesions were obtained. This was a treatment response of partial response (PR) or stable disease (SD) based on computed tomography (or magnetic resonance imaging) and AFP levels. Moreover, TACE treatment was discontinued in the presence of significant liver function deterioration or complete elimination of the liver tumors [20]. Abdomen dynamic computed tomography (or magnetic resonance imaging, alternatively) with contrast agent administration was performed, determining whether subsequent TACE treatment would be feasible.

Sorafenib treatment

Patients in the TACE + sorafenib group received continuous standard doses of sorafenib (400 mg twice a day, orally) when the liver function was close to normal, following the initial TACE procedure [21]. Patients visited the clinic every three or four weeks for AE and for tolerability assessments during sorafenib treatment. Dose adjustments were made based on clinically significant toxicity (grade 3 or 4 according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0) or the clinician's determination of patient tolerance. When grades 3 and 4 toxicities occurred, sorafenib was withdrawn until the symptoms alleviated or disappeared to grade 1 or grade 2. Sorafenib was reduced at a dose of 200 mg bid for 5 days, then increased back to 400 mg bid if patents could tolerate it well. Otherwise, sorafenib was continued at 200 mg bid [22]. Sorafenib was maintained until clinical and/or radiological progression, toxicities were intolerable or unmanageable, or until death [23].

Therapeutic effects evaluation and follow-ups

The patients were required to return to the hospital for follow-ups every 1-2 months after discharge. Liver function, blood coagulation profiles, and serum alpha-fetoprotein (AFP) levels were examined. Tumor response evaluations were performed according to the Modified Response Evaluation Criteria in Solid Tumors for HCC (mRECIST) after 6 months, rated as either complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) [25]. CTs or MRIs were used for treatment response assessment. Overall survival (OS) was calculated from the day of HCC diagnosis until the date of the final follow-up or death (no patients were lost to follow-up). Drug-related toxicity was observed and recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0. Follow-up data collection ceased in December 2017 or at patient death. No patients were lost during follow-up period.

Statistical analysis

Distribution of continuous data was assessed using Kolmogorov-Smirnov tests. Normally distributed data are presented as mean ± standard deviation and were analyzed using *t*-tests. Non-normally distributed data are presented as medians (range) and were analyzed using Mann-Whitney U-tests. Categorical variables are presented as frequencies and were analyzed using Fisher's exact tests. Survival analysis (OS) was assessed with the Kaplan-Meier method and log-rank tests. Cox's proportional hazards regression model was further conducted, analyzing the association between survival and potential risk factors, with a calculation of hazard ratios (HR) and 95% confidence intervals (CIs). SPSS 17.0 (IBM, Armonk, NY, USA) was used for all analyses. Two-sided *P*-values < 0.05 indicate statistical significance.

Results

Baseline clinical characteristics

A total of 82 patients were initially diagnosed as intermediate HCC (BCLC-B HCC) in this study. Of these, 2 cases were excluded due to exclusion criteria (HCC of Child-Pugh class C: n = 1; Complete obstruction of the portal vein: n = 1). Eventually, 80 BCLC-B HCC patients were treated with TACE in combination with sorafenib (n = 46) or with TACE alone (n = 34), respectively. The study flowchart is shown in **Figure 1**. Baseline data for both groups included age, gender, ECOG PS scores, Child-Pugh classification, tumor diameter, number of TACE interventions, serum albumin, serum total bilirubin, LDH, and AFP concentrations. Baseline data showed no statistically significant differences between the TACE + sorafenib group and TACE alone group (all P > 0.05). Results are shown in **Table 1**.

Short-term efficacy evaluation

All patients were evaluated for efficacy at the time point of 6-months of treatment according to mRECIST criteria. See **Table 2** for details.

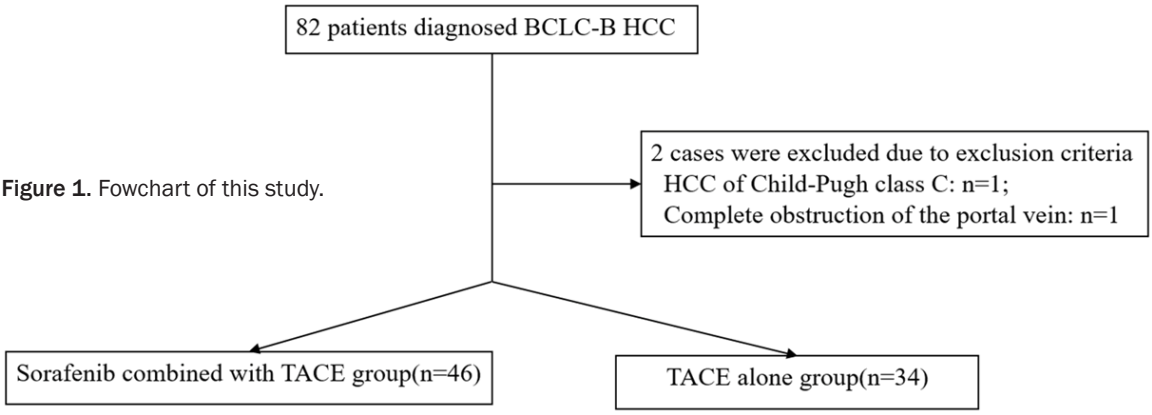

Figure 1. Fowchart of this study.

Table 1. Baseline characteristics of the patients

Variables	Sorafenib combined with TACE group (n = 46)	TACE alone group (n = 34)	*P* value
Gender			
Male	30 (65.2%)	21 (61.8%)	0.751
Female	16 (34.8%)	13 (38.2%)	
Age (Mean ± SD, years)	58.5 ± 5.7	57.6 ± 6.2	0.503
ECOG PS 0	46 (100%)	34 (100%)	NA
Child-Pugh grade			
A	31 (67.4%)	22 (64.7%)	0.802
B	15 (32.6%)	12 (35.3%)	
Tumor diameter (cm)			
≥ 6	16 (34.8%)	11 (32.4%)	0.820
< 6	30 (65.2%)	23 (67.6%)	
Serum albumin (g/L)			
≥ 35	24 (52.2%)	18 (52.9%)	0.946
< 35	22 (47.8%)	16 (47.1%)	
Serum bilirubin (umol/L)			
≥ 20	12 (26.1%)	10 (29.4%)	0.742
< 20	34 (73.9%)	24 (70.6%)	
LDH (U/L)			
≥ 245	26 (56.5%)	19 (55.9%)	0.955
< 245	20 (43.5%)	15 (44.1%)	
AFP (ng/ml)			
≥ 200	30 (65.2%)	21 (61.8%)	0.751
< 200	16 (34.8%)	13 (38.2%)	
Number of TACE			
≥ 2	24 (52.2%)	18 (52.9%)	0.946
< 2	22 (47.8%)	16 (47.1%)	

Note: TACE: Trans-arterial chemoembolization; SD: Standard deviation; ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: Lactate dehydrogenase; AFP: α-fetoprotein.

Results of short-term efficacy evaluations showed no statistically significant differences in CR rates (P = 0.068), PR rates (P = 0.859), SD rates (P = 0.794), and OR rates (P = 0.081) between patients in the sorafenib with TACE treatment group and TACE alone group. However, PD rates were significantly higher in the TACE alone treatment group than the sorafenib with TACE treatment group (P = 0.018), suggesting that TACE with sorafenib may improve short-term efficacy of BCLC-B HCC patients. Results of short-term efficacy evaluations are listed in **Table 2**.

Survival analysis

The median follow-up of the entire cohort was 24.0 (range, 6.0-40.0) months. The average age of the patients was 58.1 ± 5.0 years. Median OS was significantly longer in the TACE with sorafenib treatment group (33.0 [95% CI: 29.7-36.2] vs. 22.0 [95% 17.7-26.3] months, long rank test, P < 0.001) (**Figure 2**). The 1-, 2-, and 3-year cumulative survival rates in the TACE with sorafenib treatment group and TACE alone groups were 95.7%, 63.0%, and 34.8% vs. 94.1%, 41.2%, and 0%, respectively.

Univariate and multivariate analyses

Univariate analysis showed that OS was associated with Child-Pugh classification (HR = 5.45, 95% CI: 2.01-22.66, P = 0.03), tumor diameter (HR = 3.92, 95% CI: 1.24-12.39, P = 0.02), serum total bilirubin (HR = 3.68, 95% CI: 1.26-10.73, P = 0.017), AFP (HR = 2.67, 95% CI: 1.05-6.82, P = 0.04), and treatment methods (TACE alone or TACE with sorafenib) (HR = 0.10, 95%

Table 2. Short-term efficacy evaluation of the patients

	Sorafenib combined with TACE group (n = 46)	TACE alone group (n = 34)	*P* value
CR	15 (32.6%)	5 (14.7%)	0.068
PR	13 (28.3%)	9 (26.5%)	0.859
SD	12 (26.1%)	8 (23.5%)	0.794
PD	6 (13.0%)	12 (35.3%)	0.018
ORR	28 (60.9%)	14 (41.2%)	0.081
DCR	40 (87.0%)	22 (64.7%)	0.018

TACE: Trans-arterial chemoembolization; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; OR: Objective response; DCR: Disease control rate.

CI: 0.03-0.39, P < 0.001). Differences were statistically significant (all *P* value < 0.05), as shown in **Table 3**. Multivariate regression analysis revealed that OS was independently associated with Child-Pugh classification (HR = 5.32, 95% CI: 1.55-18.30, P = 0.008), tumor diameter (HR = 5.84, 95% CI: 1.47-23.11, P = 0.01), and treatment methods (TACE alone or TACE with sorafenib) (HR = 0.19, 95% CI: 0.07-0.47, P < 0.001). Results are shown in **Table 3**.

Analysis of adverse reactions

Table 4 lists adverse events in patients of the sorafenib with TACE treatment group and TACE alone treatment group. Adverse reactions and drug-related toxic reactions included fatigue, diarrhea, rashes, nausea, hand-foot skin reactions, hypertension, vomiting, and myelosuppression. None of the patients had toxic reactions of grade 3 or higher. In the sorafenib with TACE treatment group, the most common grade 3 adverse reactions were hand-foot skin reactions (n = 5) and hypertension (n = 4). Patients were informed of potential adverse reactions during treatment, as well as appropriate precautions for adverse reactions, supportive therapy for symptoms, and sorafenib dose adjustment regimens. Compared with patients in the TACE alone treatment group, incidence of rashes, hand-foot skin reactions, and hypertension adverse events was higher in the sorafenib with TACE treatment group than the TACE alone treatment group (all P < 0.05). However, the above toxic reactions were all within a controllable range.

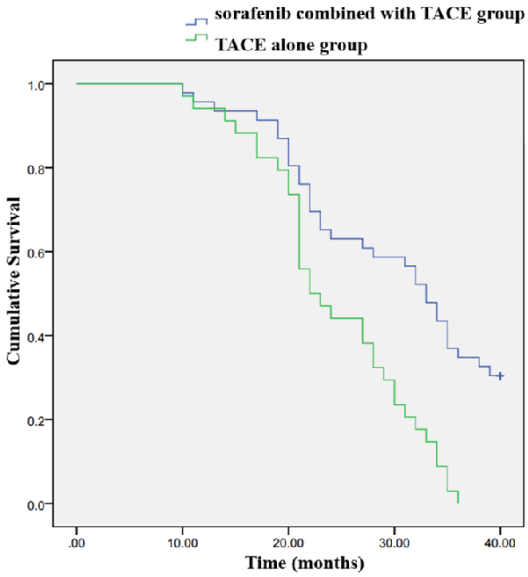

Figure 2. Overall survival of intermediate HCC (BCLC-B HCC) patients in TACE combined with sorafenib group and TACE alone group over the 3-year follow up period.

Discussion

The emergence of sorafenib has established the effectiveness of systemic therapy. It has changed the clinical concept of liver cancer treatment, promoting the development of a multidisciplinary model of local + systemic treatment of liver cancer. However, whether sorafenib can be applied to HCC patients with BCLC-B as an adjuvant therapy after hepatectomy or TACE local therapy remains unclear [26]. Numerous clinical studies have demonstrated that sorafenib has significant overall survival benefits over placebos in clinical practice [27-30] or traditional treatment strategies in advanced HCC patients [31], with acceptable safety and tolerance levels [26, 30, 32]. Sorafenib has been approved in patients with unresectable HCC based on two phase III randomized trials [33, 34]. Moreover, it is the recommended treatment for patients with advanced HCC [35, 36]. However, the efficacy of sorafenib monotherapy is generally limited, with a mean overall survival (OS) and time to progression of 10.7 and 5.5 months in the SHARP study [33], as well as 6.5 and 2.8 months in the Asia-Pacific study [34]. In addition, for HCC patients that have progressed after sorafenib treatment, whether sorafenib should be immediately withdrawn or continued remains unclear.

Table 3. Prognostic factors for overall survival in intermediate hepatocellular carcinoma (HCC) (BCLC-B) patients that received TACE + sorafenib treatment or TACE alone treatment

Variables		Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
Gender	Female	1.00	Reference				
	Male	3.71	0.47-29.23	0.21			
Age (years)							
Child-Pugh grade	A	1.00	Reference		1.00	Reference	
	B	5.45	2.01-22.66	0.03	5.32	1.55-18.30	0.008
Tumor diameter (cm)	< 6	1.00	Reference		1.00	Reference	
	≥ 6	3.92	1.24-12.39	0.02	5.84	1.47-23.11	0.01
Serum albumin (g/L)	< 35	1.00	Reference				
	≥ 35	2.78	0.91-8.54	0.07			
Serum bilirubin (umol/L)	< 20	1.00	Reference		1.00	Reference	
	≥ 20	3.68	1.26-10.73	0.017	1.75	0.67-4.57	0.26
LDH (U/L)	< 245	1.00	Reference				
	≥ 245	1.86	0.56-6.23	0.213			
AFP (ng/ml)	< 200	1.00	Reference		1.00	Reference	
	≥ 200	2.67	1.05-6.82	0.04	2.59	0.57-11.75	0.22
Number of TACE	< 2	1.00	Reference		1.00	Reference	
	≥ 2	3.25	0.86-12.33	0.08			
Treatment	TACE alone	1.00	Reference		1.00	Reference	
	TACE + sorafenib	0.10	0.03-0.39	< 0.001	0.19	0.07-0.47	< 0.001

Table 4. Adverse events of sorafenib combined with TACE group and TACE alone group

Drug-related toxicity	Sorafenib combined with TACE group (n = 46)	TACE alone group (n = 34)	*P* value
Fatigue	20 (43.5%)	11 (32.4%)	0.313
Diarrhea	15 (32.6%)	5 (14.7%)	0.068
Rash	14 (30.4%)	2 (5.9%)	0.007
Nausea	12 (26.1%)	4 (11.8%)	0.159
Hand-foot reaction	18 (39.1%)	0 (0%)	< 0.001
Hypertension	15 (32.6%)	3 (8.8%)	0.012
Vomiting	11 (23.9%)	3 (8.8%)	0.065
Bone marrow suppression	13 (28.3%)	6 (17.6%)	0.27

Some patients with HCC have progressed rapidly after treatment with sorafenib ammunition [37, 38].

For HCC patients with BCLC-B, TACE is the first choice of treatment regimens. However, TACE is not a curative treatment and the rates of objective response range from 16% to 60%, suggesting limited benefits for unresectable HCC, particularly for hypo-vascular HCC. Generally, TACE cannot result in completely necrosis of tumor lesions. TACE often induces tumor angiogenesis and further stimulates tumor growth or metastasis [40, 41]. In addition, post-TACE vascular changes and hepatic dysfunction caused by sequential TACEs ultimately limit the number of TACE treatments that a patient can receive. First, TACE intervention leads to tumors in a hypoxic microenvironment. Tumor revascularization and residual tumor proliferation may occur and develop under hypoxic conditions, thereby stimulating tumor recurrence and metastasis. Second, there is a time window for the therapeutic effects of TACE. Most patients may require several TACE repeated operations. Third, TACE can induce overproduction of VEGF, stimulating tumor progression or metastasis. Therefore, sorafenib acts on VEGF signaling pathways, inhibits angiogenesis, and has effects on inhibiting tumor cell proliferation and tumor angiogenesis. Thus, it delays disease progression in HCC patients [42]. Therefore, in recent years, some scholars have studied whether TACE with sorafenib treatment can compensate for the overproduction of VEGF after TACE intervention, improving

the therapeutic effects and benefits of patient survival [43, 44]. Arterial embolization induces hypoxic effects in tumor cells and TACE can lead to formation of transmitters for tumor neovascularization, such as the rapid release of VEGF [45, 46]. In unresectable HCC patients, VEGF levels have been verified as independent prognostic factors for prognosis [47]. Previous studies have shown that serum VEGF levels in HCC patients that received TACE treatment were gradually increased, peaking around 14 days after TACE intervention [48]. These findings support the conclusion that TACE with sorafenib treatment can improve clinical outcomes of HCC patients.

TACE treatment can cause hypoxia in tumor cells and surrounding tissues, increase expression of vascular endothelial growth factor (VEGF) by upregulating hypoxia-inducible factors, stimulate the growth of liver cancer cells, and lead to or promote the progression and metastasis of residual tumors. Sorafenib can inhibit the formation of tumor neovascularization by acting on VEGFR. Therefore, in theory, the combination of sorafenib with TACE can compensate for the overproduction of VEGF after TACE, further improving the therapeutic effects in HCC patients with BCLC-B. However, whether TACE with sorafenib treatment can improve the prognosis of HCC patients with BCLC-B remains unclear. It should be further studied in large sample, prospective, multicenter, and randomized-controlled trials.

Patients with Child-Pugh grade A were not comorbid with hepatic encephalopathy, ascites, esophageal and gastric varices bleeding, and other serious complications. In addition, patients with smaller tumor diameters had a lower tumor burden. Therefore, these factors lead to better patient prognosis and higher compliance of patients. In the past, sorafenib-related adverse reactions, along with high prices, limited their clinical application. Therefore, prevention and treatment of adverse reactions are keys to ensuring the compliance of patients. In the process of TACE with sorafenib treatment, it is recommended to take active measures to reduce incidence and degrees of adverse reactions, ensuring that patients can get the most benefit and improve the quality of life. Sorafenib-related toxic reactions in patients in this study were similar to those in previous studies [49-51]. Occurrence of these toxic reactions were all maintained within a controllable range. Most adverse reactions can be alleviated and improved by symptomatic supportive treatment and adjustments of drug doses.

There were some limitations to the current study. First, it was a retrospective study and selective bias and report bias were inevitable. Second, the sample size was relatively small. It was a single-center study. Therefore, it was not clear whether the findings in this population could not be generalized to other regions of China or other Asian countries. Well-designed multi-center, prospective, randomized, controlled trials with larger sample sizes are required to further explore risk factors that influence the prognosis of survival in BCLC-B HCC patients. Third, tumor response was just assessed at one time-point. Sequential monitoring over the follow up period would have suggested more information about the effects and safety of both treatment regimens in detail. Fourth, additional problems included whether TACE affected liver function and influenced sorafenib effects, as well as whether repeated TACE could induce *sorafenib drug resistance. These could result in tumor* recurrence and metastasis. The timing of sorafenib combined with TACE is also crucial for the improvement of life quality in patients with BCLC-B HCC. Optimal timing for TACE procedure could relieve adverse reactions and increase patient compliance.

In conclusion, results of the current study suggest that TACE with sorafenib treatment can significantly prolong mOS in HCC patients with BCLC-B, compared with TACE alone treatment. Present results provide crucial information for clinicians, suggesting that sorafenib plus TACE therapy may be a better choice than TACE treatment alone.

Disclosure of conflict of interest

None.

Address correspondence to: Yutang Chen, Department of Intervention, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang Province, China. Tel: +86-13858065532; E-mail: chenyutang_123@126.com

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