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Original Article

Efficacy of sorafenib as second-line of treatment in transcatheter arterial chemoembolization (TACE)-resistant hepatocellular carcinoma (HCC)

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Abstract: Objective: The aim of this study was to investigate the efficacy of sorafenib alone or in combination with TACE as second-line of treatment for TACE-resistant HCC. Methods: 34 TACE-resistant HCC patients received sorafenib monotherapy or in combination with TACE as a second-line treatment were reviewed retrospectively. Early tumor response was assessed according to the modified response evaluation criteria in solid tumors (mRECIST). Time to progression (TTP) and overall survival (OS) were calculated using the Kaplan-Meier method. Adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0 criteria. Results: Imaging evaluation at three months after sorafenib therapy showed complete response (CR) in 3 patients (8.8%), partial response (PR) in 10 (29.4%), stable disease (SD) in 7 (20.6%), and progressive disease (PD) in 14 (41.2%). The cumulative survival rates after initial use of sorafenib at 6, 12, and 24 months were 82%, 62%, and 36%, respectively. Specifically, these rates at months 6, 12, and 24 for patients treated with sorafenib in combination with TACE were 95%, 77%, and 45%, respectively, whereas the survival rates were 58%, 32%, and 16% for those treated with sorafenib monotherapy. Rates were significantly higher in the combination therapy group (P = 0.002). The median OS was 9 months (sorafenib monotherapy) and 25 months (sorafenib in combination with TACE) (P = 0.001), respectively. The median TTP was 5 months (sorafenib monotherapy) and 8 months (sorafenib in combination with TACE) (P = 0.058), respectively. Conclusions: Administration of sorafenib, particularly in combination with TACE, is a promising option for the treatment of TACE-resistant HCC.

Keywords: Hepatocellular carcinoma (HCC), transcatheter arterial chemoembolization (TACE), TACE-resistant, sorafenib, overall survival (OS)

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide with approximately 670,000 new cases developing per year [1, 2]. Only 10-20% of HCC patients are candidates for curative therapy [3], while most patients receive only conservative or palliative therapy, such as transcatheter arterial chemoembolization (TACE) [4-6]. Although TACE effectively delays HCC progression, the long-term survival rates still remain low due to local recurrence and distant metastasis after treatment [7, 8]. Moreover, because of tumor heterogeneity, patients do not respond uniformly to TACE therapy [9-12]. While some HCC were TACE-resistant at the beginning of the treatment, some acquired resistance to TACE after several cycles. These patients lack an effective alternative treatment, and often have a poor prognosis [13]. Thus, a new treatment strategy for TACE-resistant HCC patients is urgently needed.

Sorafenib (Nexavar, Bayer Pharmaceuticals) is an orally active, multikinase inhibitor approved by the U.S. Food and Drug Administration for the treatment of unresectable HCC [14, 15]. According to limited data [14], the European Association for the Study of the Liver and the European Organisation for Research and Treatment of Cancer (EASL-EORTC) guidelines recommended the use of sorafenib as an alternative treatment option for patients who fail to

respond to TACE [16]. However, the efficacy of this treatment strategy remains unclear.

Here, we investigate the efficacy of sorafenib monotherapy or in combination with TACE as a second-line treatment in patients with TACE-resistant HCC. Moreover, we examined the tumor response and the patient survival time after the treatment.

Patients and methods

Patient recruitment

Between April 2008 and January 2015, 34 TACE-resistant HCC patients who received sorafenib monotherapy or combination therapy with TACE as second-line treatment were retrospectively enrolled in this study. TACE-resistant HCC was defined according to the criteria of the Japanese Society of Hepatology (JSH) 2010, as tumor progression within three months after, at least, two consecutive TACE cycles [17]. The present study did not require approval in our institution for the retrospective review of patient records. All patients fulfilled the following criteria.

Inclusion criteria: 1. Patients older than 18 years of age with Barcelona Clinic Liver Cancer (BCLC) stage B at the time of initial TACE treatment therapy; 2. Patients were deemed TACE-resistant after, at least, two consecutive TACE cycles; 3. Patients diagnosed with Child-Pugh's (CP) A or B cirrhosis prior to sorafenib treatment; 4. Patients were administered sorafenib for at least for three months; 5. Written informed consent was obtained.

Exclusion criteria: 1. Patients had previously received liver resection, or liver transplant; 2. Poor performance status (Karnofsky status ≤ 70%), nutritional impairment, high serum total bilirubin levels (> 3 mg/dl).

Treatment protocol

Sorafenib was administered twice a day with a total daily starting dose of 800 mg for all patients. In the case of drug-related toxicity, several days of treatment interruption or dose reduction were allowed (400 mg QD, then 400 mg QOD). Specific laboratory parameters were monitored prior and during sorafenib treatment including complete blood cell count, blood platelet count, albumin levels, bilirubin levels, creatinine levels, and coagulation values to ensure that the patient did not have any contraindication to therapy.

The indications for TACE were as follows: 1. Computed tomography (CT) or magnetic resonance (MR) imaging showed enhancement in arterial phase of liver tumor; 2. The tumor-feeding artery was clearly visible by digital subtraction angiography (DSA) as well as technically accessible; 3. There were no TACE contraindications.

TACE was performed by injecting chemotherapeutic agents (epirubicin and oxaliplatin) that had been emulsified with lipiodol plus gelatin foam or embolization particles after superselective tumor-feeding artery catheterization. All individuals were treated as in-patients.

Follow-up

All patients were required to undergo monthly follow-ups according to the guidelines set by the China Charity Federation (CCF), which provides a free-of-cost sorafenib treatment, after three months of paid therapy at the patient's expense (http://www.ncpap.com.cn). Each follow-up session consisted of several routine laboratory tests, including liver function tests, blood tests, tumor markers - alpha-fetoprotein (AFP)-, and analysis of adverse events. Three months after initial sorafenib administration, patients were monitored by enhanced CT or MR in order to evaluate treatment response and to repeat imaging (performed on a bimonthly basis). Patients were followed either until death or until the end of the study (Dec 31, 2015).

Outcome measures

The primary outcome was tumor response. Secondary outcomes included time to progression (TTP) and overall survival (OS). Additional clinical endpoints included the rates and grade of sorafenib-related adverse events. Tumor response was measured at 3 months after the beginning of sorafenib treatment using modified response evaluation criteria in solid tumors (mRECIST). Complete response (CR) was defined as the disappearance of any intratumoral arterial enhancements in all target lesions. Partial response (PR) was defined as at least a 30% reduction in the sum of the diameters of target lesions. Stable disease (SD) was

Table 1. Patients' clinicopathological characteristics

Characteristic	Total (n = 34)	Sorafenib alone (n = 12)	Sorafenib with TACE (n = 22)	*P* value
Gender				0.491
Male	29	9	20	
Female	5	3	2	
Age (mean ± SD), yrs	54.9 ± 12.1	61.1 ± 12.0	55.2 ± 15.1	0.256
ECOG score				0.058
0-1	24	5	19	
2	10	7	3	
Virology				
B	33	12	21	0.536
C	1	0	1	
BCLC stage				0.079
B	23	6	17	
C	11	6	5	
C-P classification				0.465
A	12	3	9	
B	22	9	13	
Tumor response				
CR (%)	3 (8.8%)	0	3 (13.6%)	
PR (%)	10 (29.4%)	0	10 (45.5%)	
SD (%)	7 (20.6%)	5 (41.7%)	2 (9%)	
PD (%)	14 (41.2%)	7 (58.3%)	7 (31.8%)	
TTP (month)	5	5	8	0.058
OS (month)				
mOS_1	16.5	9	25	0.001
mOS_2	33.5	28.5	37.5	0.094

ECOG score: ECOG performance status score. TACE: Transarterial chemoembolization. BCLC: Barcelona Clinic Liver Cancer. C-P classification: Child-Pugh classification. mOS_1: median overall survival time from sequential use of sorafenib. mOS_2: median overall survival time from initial HCC diagnosis.

defined as a reduction of less than 30% or an increase of less than 20% in the target lesions with no significant newly-developed lesions. Progressive disease (PD) was defined as the appearance of new recurrent lesions, vessel invasion, distant metastasis, or an increase of at least 20% in target lesions. Time to progression (TTP) was defined as the time from the beginning of sorafenib treatment to disease progression; in some cases, it was censored at the date of the last clinical assessment. OS was defined as the survival time from either the beginning of sorafenib administration or the first diagnosis of HCC to the death of the patient, or to the end of study censoring.

Adverse events

Adverse events were assessed using the national cancer institute common terminology criteria for adverse events (NCI-CTCAE) (version 4.0). Toxicity profiles were grouped by severity (G1-G2 vs. G3-G4). The following toxicity evaluations were made: hematological tests, clinical chemistry tests, and patient discomfort symptoms, such as pain, skin reaction, diarrhea, hypertension, and fatigue.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 16.0, SPSS, Inc., Chicago, IL). Quantitative data were expressed as mean ± standard deviation when normally distributed, if not, then they were expressed as a median. Either the Student's t test (parametric test) or Mann-Whitney U test (nonparametric test) was used to compare pairs of independent, continuous variables between the groups. Either the chisquare test or Fisher's exact test was used to compare qualitative variables. TTP and OS were calculated by using the Kaplan-Meier method and were compared by using the log-rank test. Statistical significance was taken as two-sided and at *P* values less than 0.05.

Results

Study patients

During 7 years-from April 2008 to January 2015- a total of 34 HCC patients were enrolled in this study (29 men; 5 women). These patients were deemed TACE-resistant and had accepted sorafenib as second-line treatment. The diagnosis of HCC was made based on histology or imaging analysis in combination with either serum AFP levels or, at least, two coincidental imaging findings (enhanced CT, MR, or DSA) [18]. Prior to the beginning of TACE treatment, all patients were diagnosed with intermediate stage HCC (BCLC stage B). After

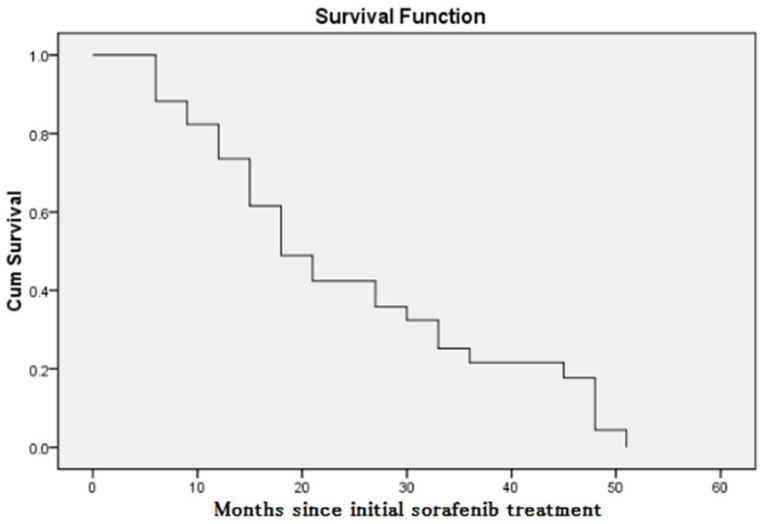

Figure 1. Kaplan-Meier survival plot shows cumulative survival rates after the initial administration of sorafenib in 34 TACE-resistant HCC patients.

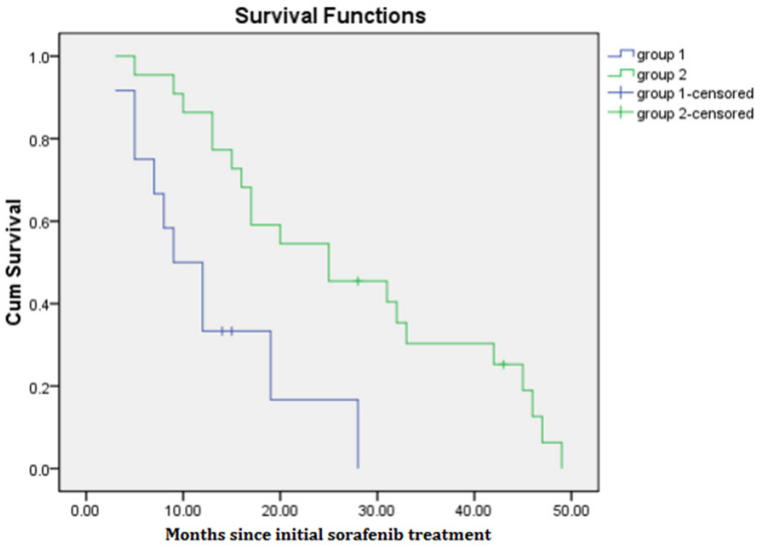

Figure 2. Kaplan-Meier survival plot for patients' overall survival (OS) according to treatment. The cumulative survival rates were significantly higher in the TACE-combined group than in the sorafenib monotherapy group (P = 0.002).

2-10 cycles of TACE treatment (mean 4.7 ± 2.1), patients were deemed TACE-resistant. Of these patients, 11 had advanced stage HCC with extrahepatic metastasis or portal vein invasion (BCLC stage C); the remaining 23 were still BCLC stage B. The mean age of these patients was 54.9 ± 12.1 years. Baseline characteristics of the 34 patients at the time of the beginning of sorafenib therapy are listed in **Table 1**.

The median time from the first TACE treatment to the initiation of sorafenib therapy was 21 months (range 4-37 months). The median follow-up time from the beginning of sorafenib treatment was 7 months (range 3-49 months). None of the patients were lost to follow-up, and all clinical encounters were completed and recorded.

Of the 34 patients, 22 received sorafenib in combination with TACE, 12 received sorafenib monotherapy due to the fact that TACE was technically inaccessible in two patients and four patients had multiple extrahepatic tumor metastasis (two patients had lung metastasis, one patient with abdominal wall metastasis and one with extensive retroperitoneal lymph node metastasis), the other 6 refused to continue TACE treatment.

Sorafenib was administered twice daily with a total daily dose of 800 mg to all patients except to six patients who showed drug intolerance and associated adverse events. These patients were changed to 400 mg QD or 400 mg QOD after interrupting sorafenib therapy for several days.

Tumor response

The first assessment was conducted three months after the start of sorafenib treatment. According to mRECIST criteria, complete response (CR) was achieved in 3 (8.8%) patients, partial response (PR) in 10 (29.4%), stable disease (SD) in 7 (20.6%), and progressive disease (PD) in 14 (41.2%). For patients who had accepted sorafenib in combination with TACE, CR was achieved in 3 (13.6%) patients, PR in 10 (45.5%), SD in 2 (9%), and PD in 7 (31.8%). In patients who accepted sorafenib monotherapy,

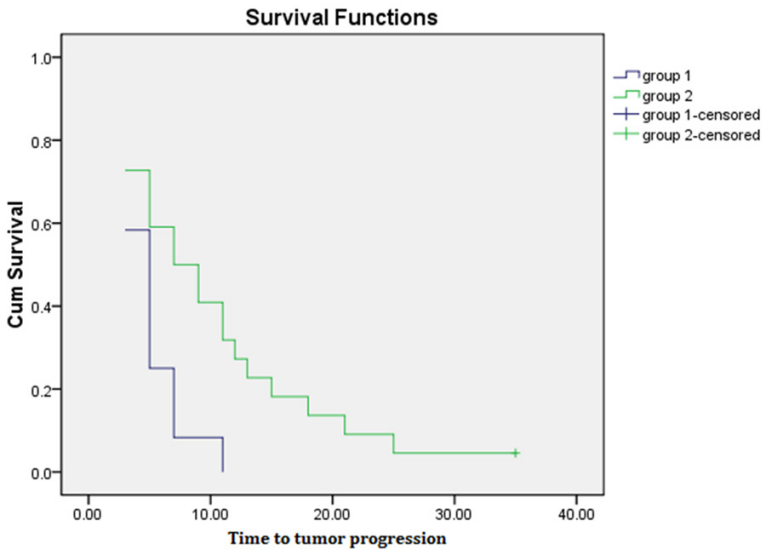

Figure 3. Kaplan-Meier survival plot for time to tumor progression (TTP) related to treatment. The median TTP tends to be higher in the TACE-combined group than in the sorafenib monotherapy group (8 months *vs.* 5 months), but statistical significance was not achieved ($P = 0.058$).

CR or PR was never achieved, and SD and PD were observed in 5 (41.7%) and 7 (58.3%) patients (**Table 1**).

Overall survival and time to progression

At the end of this study, 4 patients were still alive, and the other 30 were deceased. Survival analysis was performed using the Kaplan-Meier method. The cumulative survival rates after the start with sorafenib administration at 6, 12, and 24 months were 82%, 62%, and 36%, respectively (**Figure 1**). For patients who had accepted sorafenib in combination with TACE, cumulative survival rates at 6, 12, and 24 months were 95%, 77%, and 45%, respectively; the values were 58%, 32%, and 16% for patients who had accepted sorafenib monotherapy. The cumulative survival rates were significantly higher in patients who underwent combined therapy than in those who received sorafenib monotherapy ($P = 0.002$) (**Figure 2**).

Median overall survival time from the start of sorafenib administration (mOS_1) was 9 months in patients treated only with sorafenib and significantly higher (25 months, $P = 0.001$) in patients who received sorafenib in combination with TACE, respectively. Taking the initial HCC diagnosis as the starting point, the median overall survival time (mOS_2) was 28.5 months in sorafenib-treated patients and 37.5 months in patients who received the combined therapy. Therefore, these data showed a tendency towards a longer survival in patients who underwent sorafenib in combination with TACE ($P = 0.094$). Median TTP after sorafenib administration was 5 months after sorafenib monotherapy and 8 months in sorafenib plus TACE treatment ($P = 0.058$) (**Figure 3**).

Adverse events

In these patients, we found that sorafenib-related adverse events (AEs) were common and included hand-foot skin reaction (64.7%), diarrhea (58.8%), fatigue (44.1%), and other unwanted side effects (49.9%). Most of these adverse events were graded 1 or 2, thus, did not require dose reduction. Adverse events graded 3 or 4 occurred in 6 patients-two patient undergoing sorafenib monotherapy and four patients who received sorafenib and TACE combined treatment (**Table 2**). These patients required drug interruption and dose reduction.

Furthermore, three patients who underwent combined therapy developed severe biliary injury (mutiple intrahepatic biloma). Although percutaneous drainage was performed after biloma fomation in one of these three patients, the subject died 3 months later as a result of liver failure. The other two had no obvious symptoms (**Figures 4** and **5**).

Discussion

According to the Barcelona Clinic Liver Cancer (BCLC) staging system, transcatheter arterial chemoembolization (TACE) has been established as the standard treatment for intermediate stage HCC [6]. Despite the fact that TACE treatment has been supported by some studies, TACE does not typically result in complete tumor necrosis, since TACE induces a hypoxic environment via up-regulation of hypoxia inducible factor-1α (HIF-1), which in turn activates the expression of vascular endothelial growth

Table 2. Sorafenib-related adverse events

	Total		Sorafenib alone		Sorafenib with TACE	
	All adverse	Grade 3, 4	All adverse	Grade 3, 4	All adverse	Grade 3, 4
Hand-foot skin reaction	22 (64.7%)	1 (2.9%)	8 (66.7%)	0	14 (63.6%)	1 (4.5%)
Rash/desquamation	5 (14.7%)	0	2 (16.7%)	0	3 (13.6%)	0
Diarrhea	20 (58.8%)	5 (14.7%)	8 (66.7%)	2 (16.7%)	12 (54.5%)	3 (13.6%)
Thrombocytopenia	1 (2.9%)	0	0	0	1 (4.5%)	0
Fatigue	15 (44.1%)	0	6 (50%)	0	9 (40.9%)	0
Hypertension	1 (2.9%)	0	0	0	1 (4.5%)	0
Anorexia	9 (26.5%)	0	4 (33.3%)	0	5 (22.7%)	0
Abdominal pain	1 (2.9%)	0	0	0	1 (4.5%)	0

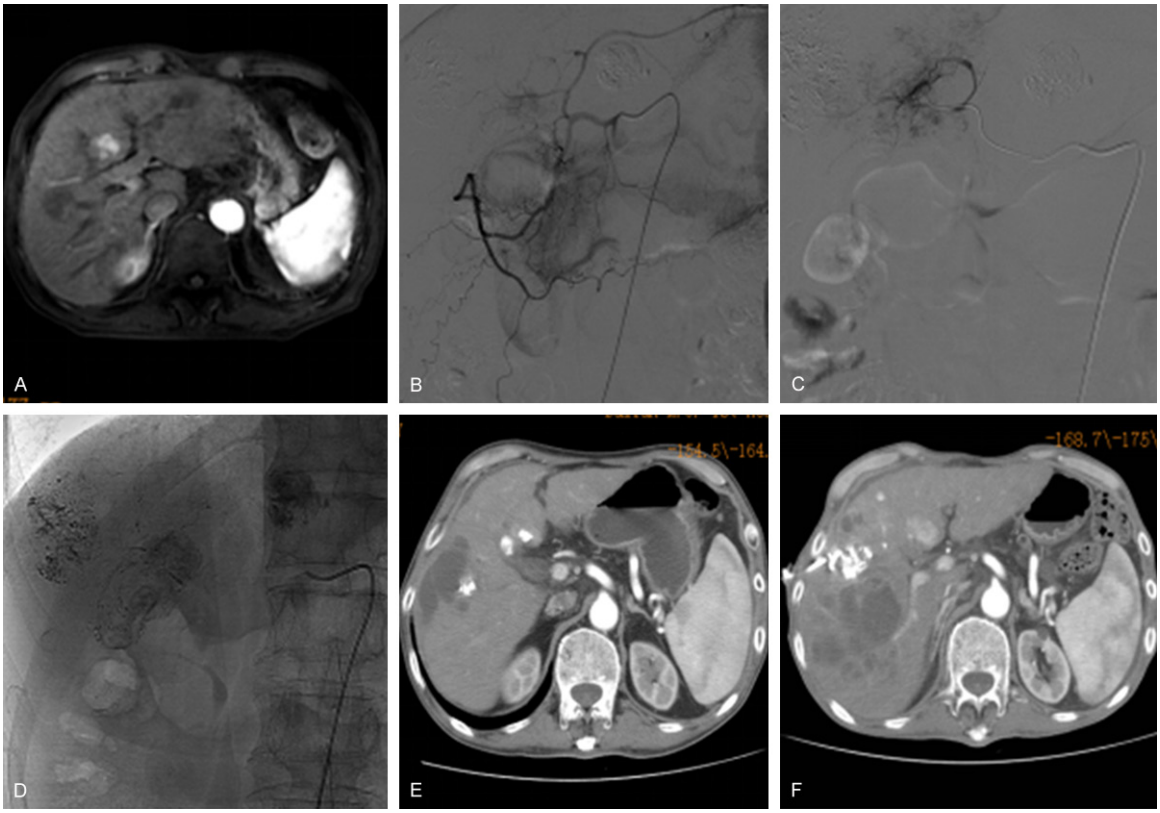

Figure 4. A 72 year-old man with TACE-resistant HCC underwent sorafenib in combination with TACE treatment for 4 years. A: MR shows lesion enhancement prior to last TACE; B-D: Superselective embolization with chemotherapeutic agents emulsified with lipiodol plus gelatin foam; E: Biloma developed two months after last TACE; F: Biliary injury aggravated and patient died three months later as a result of liver failure. Percutaneous drainage had been performed.

factor (VEGF), promoting residual tumor progression [19-21]. In the majority of HCC patients, resistance to TACE often occurs after repetitive embolization, thereby causing poor long-term survival rates. Although new chemotherapeutic drugs and embolization agents have been recently developed to improve treatment efficacy in TACE-resistant patients [22, 23], these measures have not uniformly conferred a survival advantage. Sorafenib is an orally active, multikinase inhibitor that blocks the circulating VEGF levels following TACE treatment [24]. Combined or sequential administration of sorafenib and TACE to simultaneously

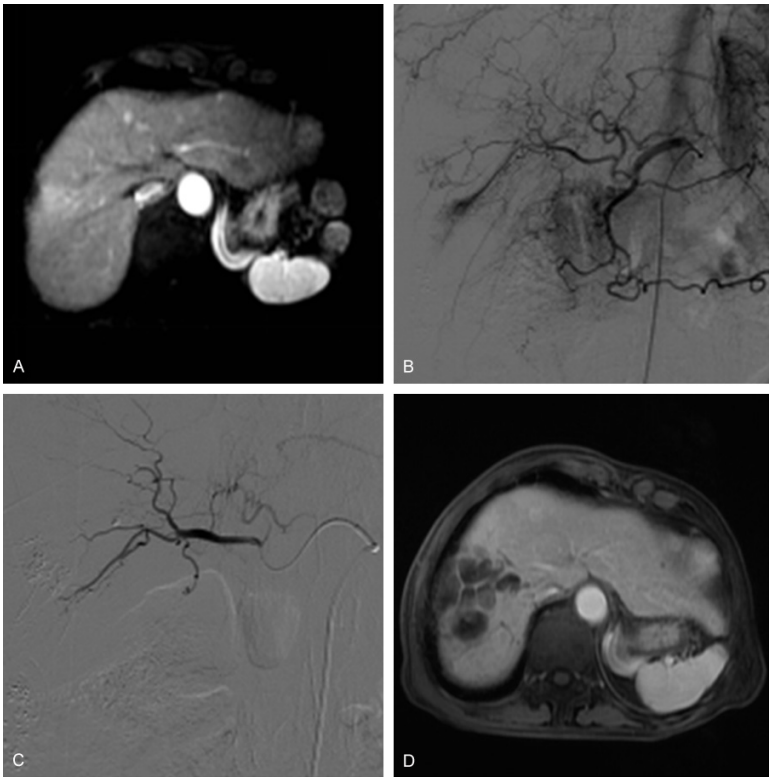

Figure 5. A 77 year-old man with TACE-resistant HCC had accepted sorafenib with TACE treatment underwent sorafenib in combination with TACE treatment for 2.5 years. Two month after last TACE cycle, the patient developed liver biloma but no obvious symptoms. A: MR shows a new enhancement lesion in segment VIII prior to last TACE; B, C: Superselective embolization with chemotherapeutic agents emulsified with lipiodol plus gelatin foam; D: Biloma developed two months after last TACE.

block proliferation and angiogenesis may be a promising treatment strategy for TACE-resistant HCC patients [25].

In this retrospective study, we tested the efficacy of sorafenib monotherapy or in combination with TACE, as second-line treatment in 34 TACE-resistant HCC patients. We obtained a 38.2% tumor response rate (CR + PR/all cases) and a 58.8% disease control rate (CR + PR + SD/all cases). These results might improve the treatment efficacy in TACE-resistant HCC patients [22, 23].

Next, we examined the data based on the therapy modality and evaluated their benefit in TACE-resistant HCC patients. Patients in the sorafenib monotherapy group showed no CR or PR. In contrast, 13.6% (3 of 22) and 45.5% (10 of 22) of patients after combined sorafenib and TACE treatment evidenced CR and PR, respectively. The tumor response rates (CR + PR/all cases) indicated that patients treated with sorafenib in combination with TACE achieved a higher tumor response rate than those treated with sorafenib monotherapy (59.1% *vs.* 0%, $P = 0.018$). Furthermore, the median survival time from the start of sorafenib treatment was longer in the combined group than in the sorafenib monotherapy group (25 months *vs.* 9 months, $P = 0.001$). The efficacy of sorafenib-TACE combined therapy was significantly better than that of sorafenib monotherapy. Ogasawara [26] demonstrated that sorafenib can prolong overall survival (OS) and time to progression (TTP) in TACE-refractory patients diagnosed with intermediate-stage HCC. Concomitantly, our data indicated that sequential administration of sorafenib, particularly in combination with TACE, can achieve a beneficial tumor response and survival in TACE-resistant HCC patients. This is a promising finding, given the lack of efficacious therapeutic options for these patients. Therefore, for patients who are candidates for TACE treatment, we recommend combined therapy with sorafenib as first treatment option.

It is important to note, however, that the median survival time calculated from the initial HCC diagnosis was 28.5 months in the sorafenib monotherapy group, and 37.5 months in the combination therapy group ($P > 0.05$). Therefore, the exact extent to which sorafenib in combination with TACE treatment will prolong patient survival compared to sorafenib monotherapy, requires further investigation. Additionally, a larger sample size for future studies is also an important variable.

TACE and sorafenib therapies, particularly when combined, may result in a number of undesirable adverse events (AEs), which may limit their applications. Compared with the SHARP study, the incidence of hand-foot skin

reaction in our study was 43.3% higher and the incidence of diarrhea 18.1% more elevated. Finally, the incidence of fatigue in our study was 20.9% higher than in the SHARP study [14]. Although the overall incidence of sorafenib-related AEs was greater in our study (90%), the incidence of grade 3/4 AEs was not higher than that reported in the SHARP study. Our findings are consistent with those reported by Liang and colleagues [27].

Different from other studies using sorafenib-TACE combination therapy for HCC [28, 29], a high rate of intrahepatic biloma formation was found in our study. Although biloma is a known risk following TACE, the high incidence of biloma formation in our study samples was not expected (13.6%, 3/22). The incidence of biloma formation in HCC patients following TACE was previously reported to occur in 0.5% to 3.3% [30-32]. Following conventional TACE, bilomas are formed due to ischemia in the peribiliary arterial plexus as a result of the deposition of chemotherapeutic agents. Although the size of our patients' cohort was very small, a rate of 13.6% in biloma formation was much higher than previously reported. The exact mechanism of the high rate of biloma formation in our study remains elusive. One possible hypothesis is that the synergistic effect of sorafenib and TACE may produce liver tissue destruction and cause ischemia in the peribiliary arterial plexus and, consequently, induce biloma formation. This particularly holds the truth for patients who received multiple cycles of TACE in combination with sorafenib therapy. It is important to take into consideration that, when TACE is combined with sorafenib, the placement of the micro-catheter must be superselective, and should avoid as much as possible chemotherapeutic agents' overembolization and non-target embolization to avoid biliary ischemia.

The main limitations of our study include its retrospective design and the small number of patients included. Our results require confirmation in a larger, well-designed clinical trial, including a long enough follow-up period to demonstrate an OS advantage.

Conclusions

Our data indicate that sorafenib, particularly in combination with TACE, holds promise as a second-line treatment option for TACE-resistant HCC patients.

Disclosure of conflict of interest

None.

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