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ORIGINAL ARTICLE

Efficacy of sorafenib combined with transcatheter hepatic arterial chemoembolization in treating intermediate-advanced hepatocellular carcinoma

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Summary

Purpose: *To explore the efficacy and safety of sorafenib combined with transcatheter hepatic arterial chemoembolization (TACE) in the treatment of intermediate-advanced hepatocellular carcinoma (HCC).*

Methods: *A total of 132 intermediate-advanced HCC patients were divided into two groups, namely, control group (n=66, TACE) and Sorafenib group (n=66, TACE combined with sorafenib). Then, the clinical efficacy and incidence rate of adverse reactions were compared s. Besides, the levels of tumor markers and liver function indicators were detected before and after treatment. Additionally, the survival of patients was followed up and recorded.*

Results: *The overall response rate (ORR) and clinical benefit rate (CBR) were significantly higher in Sorafenib group than those in control group. Both Sorafenib group and control group exhibited significantly lowered levels of serum AFP, CEA, CA125 and CA19-9 after treatment compared with those before treatment. In addition, such levels were prominently lower in Sorafenib group than those in control group after treatment. Compared with those before treatment, the levels of total bilirubin (TBil) and alanine aminotransferase (ALT), liver function indexes, significantly rose, while the albumin (Alb) level had no obvious changes in the two groups after treatment. Besides, the liver function indexes displayed no statistically significant differences between the two groups after treatment. Based on the results of follow-up, the median overall survival (OS) and 3-year OS were 16.83 months and 25.8% in Sorafenib group and 12.48 months and 15.2% in control group, respectively.*

Conclusion: *Sorafenib combined with TACE achieves better clinical efficacy in the treatment of intermediate-advanced HCC in contrast with TACE alone, which is able to significantly reduce the levels of serum tumor markers and prolong the survival of patients, and results in tolerable adverse reactions.*

Key words: *Sorafenib, transcatheter hepatic arterial chemoembolization, hepatocellular carcinoma, intermediate-advanced stage, efficacy*

Introduction

Due to the insidious onset, high malignancy and quick progress of liver cancer, the majority of such patients have been diagnosed with intermediate-advanced liver cancer at the first clinic visit. As to the treatment of intermediate-advanced liver cancer, transcatheter hepatic arterial chemoembolization (TACE) is recommended currently [1,2]. TACE has been reported in a meta-analysis on previous randomized controlled trials to be able to dramatically improve the short-term survival rate of patients [3,4]. However, TACE leads to ischemia and hypoxia of tumors, which will feed back and trigger the increase in the level of vascular endothelial cell growth factors (VEGFs), further stimulating the

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formation of tumor blood vessels to result in tumor recurrence and metastasis. Hence, the long-term clinical efficacy of TACE remains unsatisfactory [5]. Sorafenib, a multi-targeted, oral and systemic anti-tumor drug, can suppress VEGF receptors (VEGFRs) to block the formation of tumor blood vessels, inhibiting the growth of tumor cells [6,7]. The results of comparative studies have manifested that in the treatment of intermediate-advanced liver cancer, TACE combined with sorafenib is more effective than sorafenib or TACE alone, which is also safe and well tolerated [7,8]. In this study, the efficacy and safety of sorafenib combined with TACE in the treatment of intermediate-advanced hepatocellular carcinoma (HCC) were probed into, hoping to offer a strong basis for the selection of clinical therapeutic regimens for such patients

Methods

Study subjects

A total of 132 patients with intermediate-advanced HCC admitted to our hospital from May 2016 to October 2017 were enrolled as study subjects, and their clinical data were collected. The inclusion criteria were set as follows: 1) patients meeting the diagnostic criteria for clinical HCC, 2) those with at least one measurable and untreated lesion assessed based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST), 3) those with Barcelona Clinic Liver Cancer Stage B or C HCC, 4) those with liver function of Child-Pugh Class A or B, 5) those with a ECOG score of 0-2 points, and 6) those having not received any other anti-tumor treatments. The exclusion criteria involved: 1) patients with liver function of Child-Pugh Class C, complete blockage of the main portal vein and refractory ascites, 2) those with dysfunction of important organs including the heart, liver, lungs and kidneys, 3) those taking immunosuppressants or glucocorticoids for a long time, 4) those with mental disorders, 5) those allergic to drugs, 6) those with coagulation dysfunction or bleeding tendency, or 7) those with other malignant tumors. Among the 132 patients, there were 104 males and 28 females aged 39-77 years old, with a mean of (59.24±10.25) years old. The baseline data displayed no statistically significant differences between the two groups of patients ($p>0.05$), which were comparable (Table 1). All patients enrolled were informed and signed the informed consent approved by the Ethics Committee of the hospital in accordance with the *Declaration of Helsinki*.

Therapeutic methods

The right femoral artery was punctured *via* the Seldinger technique, and a catheter was inserted for coeliac and superior mesenteric angiography, so as to determine the location, size, number and blood supply of tumors

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Sorafenib group (n=66)* *n (%)*	*Control group (n=66)* *n (%)*	*p*
Gender (Male/Female)	49/17	55/11	0.287
Age (years)	60.46±9.91	58.97±10.52	0.404
Largest tumor diameter (cm)	5.23±2.49	5.41±2.31	0.668
Number of tumor lesions			0.252
1	16 (24.2)	23 (34.8)	
≥2	50 (75.8)	43 (65.2)	
Distant metastasis (n, %)	11 (16.7)	8 (12.1)	0.621
BCLC staging			0.478
B	29 (43.9)	24 (36.4)	
C	37 (56.1)	42 (63.6)	
Child-Pugh class			0.627
A	37 (56.1)	34 (51.5)	
B	29 (43.9)	32 (48.5)	
AFP (μg/L)			0.480
≤400	30 (45.5)	25 (37.9)	
>400	36 (54.5)	41 (62.1)	
Portal vein tumor thrombus	17 (25.8)	21 (31.8)	0.565
ECOG score			0.395
0	14 (21.2)	17 (25.8)	
1	35 (53.0)	29 (43.9)	
2	17 (25.8)	20 (30.3)	

BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha fetoprotein; ECOG: Eastern Cooperative Oncology Group.

and understand portal patency. Through super-selective catheterization to the feeding artery of tumors, infusion chemotherapy with lobaplatin 20-40 mg/m^2 + epirubicin 20-40 mg/m^2 and ultra-fluid lipiodol suspension was carried out. After that, the feeding vessel of tumors was embolized with gelatin sponge particles. After surgery, patients were given routine symptomatic treatments including liver protection, stomach protection and hydration. At 1 month after surgery, patients underwent computed tomography (CT) scan to evaluate the effect of tumor embolization. TACE would be conducted again if tumors had residual activity. If there were dense lipiodol deposition in lesions, necrosis of tumor tissues, and no new lesions or progress, TACE would be stopped, and CT examination was performed every 2 months. TACE would be carried out if the results of CT examination suggested tumor recurrence.

From the 3rd day after TACE, patients took sorafenib (product name: Nexavar, manufacturer: Bayer Pharma AG, approval number: H20130137, specification: 200 mg/tablet) at 400 mg/time, 2 times/day. Sorafenib was suspended before repeated TACE and given at the original dose from the 2nd day after TACE. Next, patients were followed up to observe adverse drug reactions. If there were grade 3 adverse reactions, and patients could not tolerate them, the dose of sorafenib was reduced to 400 mg/time, once a day or every other day. Sorafenib was recommended to be discontinued if there were disease progress or exacerbation, serious adverse reactions, and hepatic decompensation (Child-Pugh Class C).

Observation indexes

The clinical efficacy was assessed based on the results of enhanced abdominal CT, blood routine, liver function, and alpha-fetoprotein (AFP) examinations conducted every 2 months using the mRECIST, including complete remission (CR): all lesions disappear or their functional activity disappears completely, partial remission (PR): the maximum diameter of lesions is reduced by ≥30%, stable disease (SD): the maximum diameter of lesions declines by <30% and rises by ≤20%, and progressive disease (PD): the maximum diameter of *in situ* lesions is increased by >20% or new lesions or extrahepatic metastases are found. Response rate (RR) = number of (CR + PR) cases / total number of cases ×100%. The adverse reactions were classified *as per* the National Cancer Institute CTCAE 4.0.

The levels of tumor markers AFP, carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125) and CA19-9 were compared between the two groups of patients before and after treatment. Fasting venous blood (5 mL) was collected from patients in the morning before and after treatment and centrifuged at 2,500 rpm for 10 min, followed by separation of the serum in which the tumor markers were detected *via* electrochemiluminescence. Besides, the levels of liver function indexes albumin (Alb), total bilirubin (TBil) and alanine aminotransferase (ALT) were compared between the two groups of patients before and after treatment. Fasting venous blood (5 mL) was collected from patients in the morning for determining liver function indicators using an automatic biochemistry analyzer (CL-7300, Shimadzu).

The patients were followed up to record the survival until September 2020. Overall survival (OS) refers to the time interval from the start of treatment to the time of death or deadline of follow-up.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was utilized for statistical analysis. The measurement data were expressed as mean ± standard deviation, and t-test was employed for the comparison between the two groups. The enumeration data were expressed as ratio (%), and compared *via* x^2 test or Fisher's exact test. The paired data of immunological indexes were analyzed by t-test within the group and compared *via* two-way analysis of variance (ANOVA) between the two groups. Survival curves were plotted using Kaplan-Meier method, and log-rank test was employed. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of clinical efficacy between two groups of patients after treatment

In Sorafenib group (n=66), there were 6 cases of CR, 30 cases of PR, 16 cases of SD and 14 cases of PD, with an overall RR (ORR) of 54.5% (36/66) and a clinical benefit rate (CBR) of 78.8% (52/66). In control group (n=66), there were 3 cases of CR, 21 cases of PR, 16 cases of SD and 26 cases of

Table 2. Clinical effective rates of the two studied groups

	Sorafenib group (n=66) *n (%)*	*Control group (n=66)* *n (%)*	*p*
CR	6 (9.1)	3 (4.5)	
PR	30 (45.5)	21 (31.8)	
SD	16 (24.2)	16 (24.2)	
PD	14 (21.2)	26 (39.4)	
ORR	36 (54.5)	24 (36.4)	0.036
CBR	52 (78.8)	40 (60.6)	0.023

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate; CBR: clinical benefit rate.

PD, with an ORR of 36.4% (40/66) and a CBR of 60.6% (40/66). The ORR and CBR were significantly higher in Sorafenib group than those in control group, showing statistically significant differences (p=0.036, p=0.023) (Table 2).

Comparisons of serum tumor marker levels between two groups before and after treatment

The levels of serum AFP, CEA, CA19-9 and CA125 were (619.51±59.63) μg/L, (3.59±0.66) μg/L, (68.48±7.17) U/mL and (78.67±8.72) U/mL in Sorafenib group and (626.38±61.61) μg/L, (3.56±0.69) μg/L, (69.16±7.09) U/mL and (77.58±8.11) U/mL in control group, respectively. After treatment, they declined to (80.68±19.73) μg/L, (2.21±0.63) μg/L, (30.33±5.84) U/mL and (39.61±4.89) U/mL in Sorafenib group and (117.74±23.62) μg/L, (2.51±0.71) μg/L, (34.64±6.10) U/mL and (44.29±5.15) U/mL in control group, respectively. After treatment, the levels of serum tumor markers were signally lower in Sorafenib group than those in control group, with statistically significant differences (p<0.001, p=0.011, p<0.001, p<0.001) (Figure 1).

Comparisons of liver function indexes between two groups of patients before and after treatment

The serum ALT level was increased from (48.12±4.64) U/L and (47.80±4.14) U/L before treatment to (57.79±5.59) U/L and (59.15±5.08) U/L after treatment in Sorafenib group and control group, respectively. The Alb level rose from (40.88±2.65) g/L and (40.24±2.49) g/L before treatment to (41.92±2.47) g/L and (42.32±2.58) g/L after treatment, respectively. The TBil level was elevated from (16.10±2.16) μmol/L and (15.85±2.12) μmol/L to (18.68±2.54) μmol/L and (19.03±2.06) μmol/L. These levels had no statistically significant differences between the two groups before and after treatment (p>0.05).

Comparison of incidence rate of adverse reactions between two groups of patients

The TACE-related adverse reactions (fever, hepatalgia, nausea and vomiting and gastrointestinal bleeding) displayed no statistically significant differences between the two groups (p>0.05), which generally lasted for 5-7 d and were relieved after internal medicine symptomatic treatment. Such

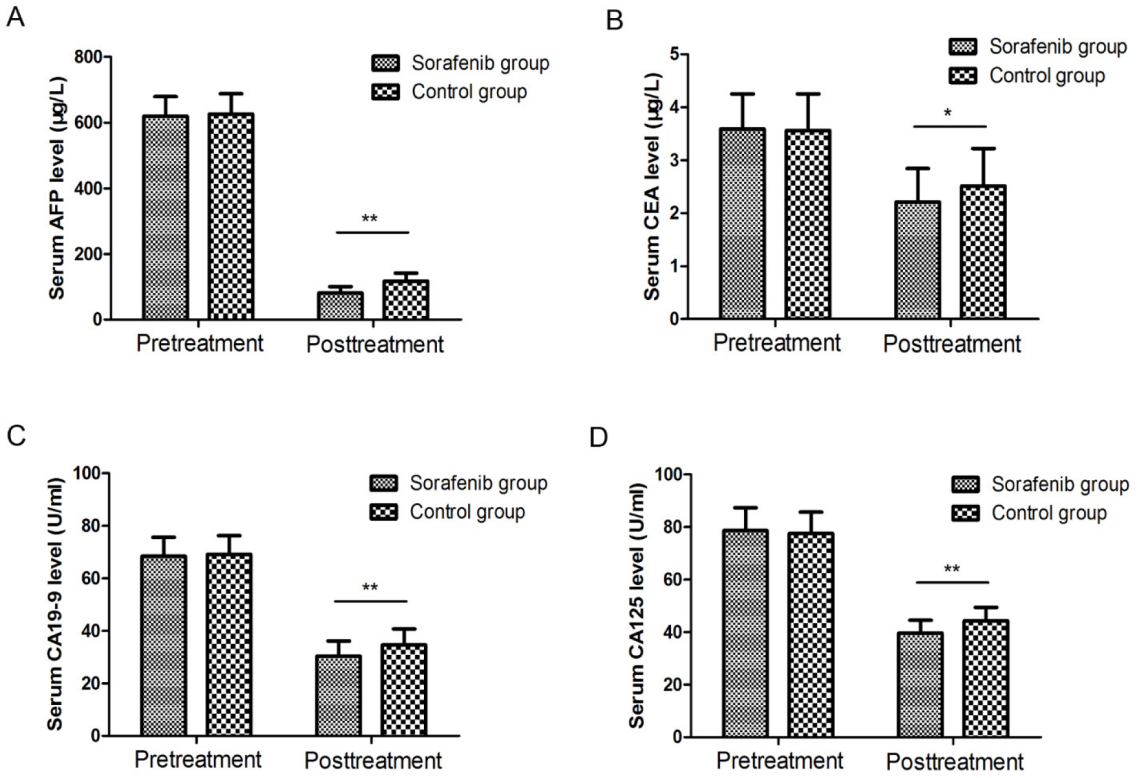

Figure 1. Comparison of serum AFP, CEA, CA19-9 and CA125 levels of patients in the two groups. Pretreatment AFP **(A)**, CEA **(B)**, CA19-9 **(C)** and CA125 **(D)** levels of patients had no significant difference between Sorafenib group and Control group (p=0.516, p=0.699, p=0.585, p=0.459). Posttreatment serum AFP **(A)**, CEA **(B)**, CA19-9 **(C)** and CA125 **(D)** levels of patients in both groups dramatically decreased after treatment (p<0.05). Posttreatment serum AFP **(A)**, CEA **(B)**, CA19-9 **(C)** and CA125 **(D)** levels of patients in Sorafenib group were significantly lower than those of Control group respectively (*p<0.05, **p<0.01).

Table 3. Comparison of adverse reactions of patients in the two studied groups

	Sorafenib group (n=66) *n (%)*	*Control group(n=66)* *n (%)*	*p*
Hepatalgia	19 (28.8)	22 (33.3)	0.573
Fever	12 (18.2)	15 (22.7)	0.517
Nausea and vomiting	18 (27.3)	14 (21.2)	0.416
Diarrhea	9 (13.6)	7 (10.6)	0.594
Alopecia	20 (30.3)	16 (24.2)	0.434
Loss of appetite	24 (36.4)	19 (28.8)	0.353
Gastrointestinal bleeding	2 (3.0)	3 (4.5)	0.648
Jaundice	13 (19.7)	17 (25.8)	0.406
Ascites	10 (15.2)	8 (12.1)	0.612
Stomatitis	12 (18.2)	7 (10.6)	0.215
Hypertension	9 (13.6)	13 (19.7)	0.350
Hand-foot syndrome	25 (37.9)	16 (24.2)	0.091

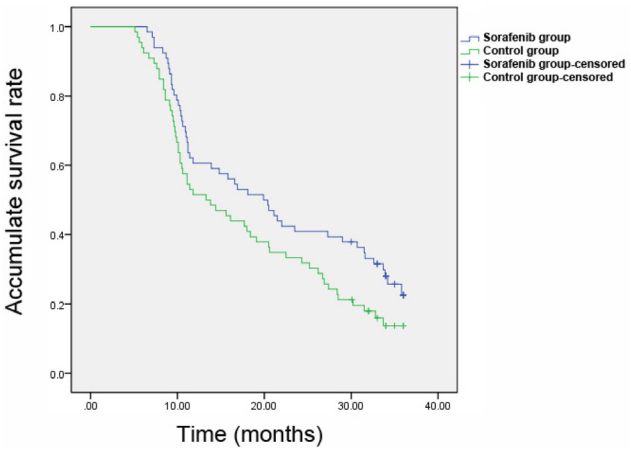

Figure 2. Kaplan-Meier survival curves of patients in Sorafenib group and Control group. The overall survival rate of patients in Sorafenib group was significantly higher than that of Control group (p=0.044).

severe complications as liver abscess, gastrointestinal perforation and liver and kidney failure were not observed. In observation group, the major sorafenib-associated adverse reactions found were hand-foot syndrome, alopecia, diarrhea, hypertension and loss of appetite, which were grade 3 and below and basically attenuated after symptomatic treatment. Besides, grade 3 hypertension was detected in 1 patient, who was given medical antihypertensive treatment after the drug was suspended for a short time, and the drug dose was then restored to the original dose. In addition, 5 patients had intolerable grade 3 hand-foot syndrome and diarrhea, and their drug dose was reduced to 400 mg/d (Table 3).

Follow-up results of patients' survival

Up to September 2020, the patients were followed up for 5-36 months, with a median follow-up time of 29.3 months. The median OS was 16.83 months and 12.48 months, 1-year OS was 60.6% (40/66) and 51.5% (34/66), 2-year OS was 40.9%. (27/66) and 33.3% (22/66), and 3-year OS was 25.8% (17/66) and 15.2% (10/66) in Sorafenib group and control group, respectively. Survival curves were plotted by Kaplain-Meier method (Figure 2). The results of Log-rank test revealed that the OS of patients was clearly superior in Sorafenib group to that in control group (p=0.044).

Discussion

Clinically, surgical resection is mainly adopted for the treatment of early liver cancer, while patients with intermediate-advanced liver cancer are largely treated with radiotherapy and chemotherapy since they have lost the best operation opportunity. As the recommended non-surgical treatment approach in clinic at present [9], TACE can increase the local chemotherapeutic drug concentration in tumors by directly injecting drugs into tumor lesions through the catheter, thus killing tumor cells more effectively. Besides, TACE results in ischemic necrosis of tumor cells by embolizing local blood vessels to block the blood supply to tumor cells, thereby better killing tumor cells. In addition, TACE also reduces the time of chemotherapy drugs in the vein and incidence rate of complications caused by chemotherapy drugs, and improves the treatment tolerance of patients [3,10]. However, TACE

alone achieves limited efficacy, with a relatively high postoperative recurrence rate in patients. This may be because TACE leads to hypoxia of tumor tissues and irritably induces the production of VEGFs in quantity, resulting in tumor neovascularization [11]. For this reason, drugs against tumor neovascularization are used after TACE, which becomes a vital combination therapy of TACE.

Sorafenib is a multi-kinase inhibitor taken orally, which treats tumors by exerting the inhibitory effects of many tyrosine kinase receptors (mainly including VEGFR-2, platelet-derived growth factor receptor-β, VEGFR-3, and the Raf family of threonine and serine protein kinases) in the body [12,13]. This shows that sorafenib can effectively improve the angiogenesis of tumor tissues, which can just make up for the deficiency of TACE, i.e., TACE promotes the angiogenesis of tumor tissues. Therefore, there is a good theoretical basis for the treatment of liver cancer by sorafenib combined with TACE. A study conducted by Wan et al., in which 744 liver cancer patients unable to receive surgical resection were enrolled, showed that the median survival time and 1-, 2- and 3- OS of patients treated with sorafenib combined with TACE and those undergoing TACE alone are 20.23 months, 62.73%, 43.96% and 31.03%, and 13.97 months, 54.93%, 34.40% and 22.27%, respectively, suggesting that the combined treatment can prolong the survival time [14]. The results of some Meta analyses uncovered that the application of sorafenib combined with TACE prolongs the median survival time and median time to tumor progression of patients, achieving certain therapeutic effects, but it has no effect on progression-free survival [15,16]. In addition, it is found in other Meta analyses that the application of sorafenib combined with TACE prolongs only the time to tumor progression of patients, without extension of progression-free survival [17-19]. In this study, it was found that the ORR and CBR were significantly higher in Sorafenib group than those in control group (p=0.036, p=0.023). The results of the 5-36 months of follow-up revealed that the median OS was 16.83 months in Sorafenib group and 12.48 months in control group. Based on log-rank test, the OS of patients was clearly longer in Sorafenib group than that in control group (p=0.044). The reason may be that sorafenib and TACE act in synergy, jointly exerting the anti-tumor effect, and sorafenib can reduce tumor metastasis and recurrence caused by TACE.

AFP, CEA, CA125 and CA19-9 are common tumor markers in clinic. AFP is a more sensitive for diagnosing primary liver cancer, and positive AFP is found in 3/4 of patients with primary liver cancer. CA125 and CA19-9, tissue-specific antigens, have high expressions in tumor tissues and no expressions in normal tissues, which are conducive to the diagnosis of tumor patients and the determination of prognosis [20,21]. In this study, it was uncovered that the levels of AFP, CEA, CA125, and CA19-9 were significantly lowered in the two groups of patients after treatment compared with those before treatment, and the reductions were larger in Sorafenib group, implying the good value of sorafenib combined with TACE in treating intermediate-advanced liver cancer. Besides, after treatment, the levels of liver function indexes ALT and TBil in the two groups of patients were significantly higher than those before treatment, but they had statistically significant differences between the two groups, while the Alb level showed no obvious changes in the two groups of patients. In addition, Sorafenib group had a lower incidence rate of adverse reactions in comparison with control group, further indicating that sorafenib combined with TACE is safe and effective in the treatment of intermediate-advanced liver cancer, without increases in the liver function damage and adverse reactions in patients.

There are some shortcomings in this study. For instance, the sample size was small, the follow-up time was short, and the tumor progression of patients was not followed up and analyzed. Hence, multicenter and large-sample prospective randomized studies are needed in the future to verify the conclusion made in this study.

Conclusion

Sorafenib combined with TACE achieves better clinical efficacy and results in tolerable adverse reactions in the treatment of intermediate-advanced HCC in contrast with TACE alone, which evidently reduces the level of serum tumor markers and prolongs the survival of patients.

Conflict of interests

The authors declare no conflict of interests.

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