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ORIGINAL ARTICLE

Sorafenib combined with transarterial chemoembolization prolongs survival of patients with advanced hepatocellular carcinoma

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Summary

Purpose: *To explore the efficacy and safety of sorafenib combined with transarterial chemoembolization (TACE) in the treatment of advanced hepatocellular carcinoma.*

Methods: *118 patients with advanced hepatocellular carcinoma treated in our hospital from June 2014 to June 2016 were collected and randomly divided into the Sorafenib+TACE group (treated with Sorafenib combined with TACE, n=59) and the TACE group (n=59). The clinical efficacy, the changes in levels of serum vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and alpha fetoprotein (AFP) before and after treatment, adverse reactions and postoperative survival of patients were observed and recorded.*

Results: *The objective response rate (ORR) and the disease control rate (DCR) were 55.9% (33/59) and 86.4% (51/59) in the Sorafenib+TACE group, and 37.3% (22/59) and 67.8% (40/59) in the TACE group. Both ORR and DCR in the Sorafenib+TACE group were significantly superior to those in the TACE group (p=0.022, p=0.027). Main adverse reactions after treatment included myelosuppression, fever, rash, gastrointestinal reactions, hepatalgia, hypertension and hand-foot syndrome, mostly of grade I-II, which were all improved after dose reduction and symptomatic treatment. The incidence rates of rash, diarrhea, hypertension and hand-foot syndrome in the Sorafenib+TACE group were obviously higher than those in the TACE group (p<0.001, p=0.002, p=0.002, p<0.001). The levels of serum VEGF, bFGF and AFP declined significantly in both groups after treatment compared with those before treatment (p=0.013, p<0.001, p<0.001), while they were evidently lower in the Sorafenib+TACE group than in the TACE group after treatment (p<0.001, p=0.016, p<0.001). Follow-up results showed that the overall survival in the Sorafenib+TACE group was significantly longer than in the TACE group (p=0.030).*

Conclusion: *Compared with TACE alone, Sorafenib combined with TACE can significantly improve ORR and DCR, obviously reduce the levels of serum VEGF, bFGF and AFP, and prolong the survival of patients with advanced hepatocellular carcinoma, while the adverse reactions are tolerable, so it is worthy of clinical popularization and application.*

Key words: *sorafenib, transarterial chemoembolization, hepatocellular carcinoma, advanced stage, efficacy*

Introduction

Hepatocellular carcinoma is one of the most common malignant tumors in China, characterized by insidious onset, high grade of malignancy and rapid progression, and most patients have been in advanced disease stage at the time of initial diagnosis, thus losing the opportunity of operative treatment [1]. Transarterial chemoembolization (TACE) is currently the preferred treatment for advanced liver cancer [2]. A meta-analysis of previous randomized controlled trials showed that TACE can significantly improve the short-term survival of patients [3,4]. In TACE, the feeding artery of tumor is blocked using the embolic agent, so that local ischemia and hypoxia are caused in tumors and the

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tumor cell growth is inhibited, thereby inducing necrosis and apoptosis of tumor cells. However, TACE cannot achieve total necrosis of lesions, but can promote the activation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), and facilitate neovascularization, leading easily to tumor recurrence and metastasis [5,6]. Such limitations make the long-term clinical efficacy of TACE unsatisfactory.

Sorafenib is a multi-targeted oral systemic antitumor drug, which can directly inhibit tumor proliferation through suppressing its downstream signaling pathway, and block tumor angiogenesis through inhibiting angiogenic factors such as VEGF and bFGF, thus indirectly inhibiting the growth of tumor cells [7]. In recent years, it has been reported that the efficacy of Sorafenib combined with TACE is superior to that of Sorafenib or TACE alone in the treatment of advanced liver cancer, and it is safe and tolerable [8,9]. To further evaluate the efficacy and safety of Sorafenib combined with TACE in the treatment of liver cancer patients in China, the clinical data of 118 patients with advanced liver cancer treated in our hospital from June 2014 to June 2016 were retrospectively analyzed, and the patients were treated with Sorafenib combined with TACE and TACE alone, which is expected to provide a more scientific basis for the development of effective therapeutic regimens.

Methods

General data

This study was approved by the Ethics Committee of our hospital. Signed informed consents were obtained from all participants before the study entry. A total of 118 patients with advanced hepatocellular carcinoma treated in our hospital from June 2014 to June 2016 were selected for the study. The diagnostic criteria were based on the *Expert Consensus on Standardization of the Management of Hepatocellular carcinoma* developed by the Chinese Society of Liver Cancer and Chinese Society of Clinical Oncology, Chinese Anti-Cancer Association, and Liver Cancer Study Group, and Chinese Society of Hepatology, Chinese Medical Association. The patients included were 69 males and 49 females, aged 24-73 years with an average of 57.64±10.77 years. The number of tumors was 1 in 79 cases and 2 or more in 39 cases.

Inclusion criteria: patients definitely diagnosed with hepatocellular carcinoma according to the diagnostic criteria, those in the Barcelona clinic liver cancer (BCLC) stage B-C and liver function Child-Pugh grade A-B, those with the Eastern Cooperative Oncology Group (ECOG) score ≤2 points and at least 1 measurable lesion, those undergoing no interventional therapy (TACE and micro-

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

Parameters	*Sorafenib+TACE group (n=59) n (%)*	*TACE group (n=59) n (%)*	*p value*
Gender (male/female)	37/22	32/27	0.096
Age (years)	56.31±9.87	58.11±10.44	0.338
Number of tumors			0.696
1	38 (64.4)	41 (69.5)	
≥2	21 (35.6)	18 (30.5)	
Size of tumors (cm)			0.574
<5	26 (44.1)	22 (37.3)	
≥5	33 (55.9)	37 (62.7)	
BCLC staging			0.354
B	30 (50.8)	36 (61.0)	
C	29 (49.2)	23 (39.0)	
Child-Pugh class			0.381
A	43 (72.9)	48 (81.4)	
B	16 (27.1)	11 (18.6)	
AFP (ng/mL)			0.493
≥400	14 (23.7)	10 (16.9)	
< 400	45 (76.3)	49 (83.1)	
ECOG score			0.348
0	34 (57.6)	39 (66.1)	
1	25 (42.4)	20 (33.9)	

TACE: Transcatheter arterial chemoembolization; BCLC: Barcelona Clinic Liver Cancer; AFP: alpha fetoprotein; ECOG: Eastern Cooperative Oncology Group

wave ablation) and targeted therapy for liver cancer, and those with an estimated survival time of >3 months.

Exclusion criteria: patients who underwent interventional therapy or other treatments within 3 months, those with contraindications to TACE, those with severe hepatic, renal or cardiac dysfunction, those with bleeding tendency or coagulation disorders, those allergic to the drugs used in this study, pregnant or lactating women. There were no statistically significant differences in the age, gender, number of tumors, tumor size, BCLC stage, liver function Child-Pugh grade and preoperative ECOG score between the two groups (p>0.05) (Table 1). All patients enrolled adhered to the *Declaration of Helsinki*, and signed the informed consent.

Treatment methods

All patients underwent TACE: After routine local anesthesia, the femoral artery was punctured using the Seldinger technique, and arteriography was performed for the celiac axis and hepatic artery using 5F-RH catheter. After the tumor size, site, number and blood supply were determined, TACE was performed using an appropriate regimen. Oxaliplatin (80-100 mg), epirubicin (10-20 mg) and 5-fluorouracil (0.5-1.0 g) were used as the chemotherapy drugs, and the emulsifier mixing iodized oil and epirubicin as the embolic agent. According to the tumor size and blood supply in patients, the drug dosage was adjusted and the diffusion of iodized oil in the hepatic region around the tumor during chemotherapy was used as the standard for the termination of embolization. TACE needed to be performed for several times based on the condition of disease, at an interval of 4 weeks.

On the basis of TACE, the patients in the Sorafenib+TACE group took orally 400 mg of Sorafenib Tosylate tablets (trade name: Duojimei, approval No.:H20130137, Bayer Pharma, Germany) twice a day from 1 week after TACE. In the case of intolerable adverse reactions, the dose could be reduced to 400 mg/day, and the administration dosage was determined according to the relief degree of adverse reactions. During treatment, liver-protecting treatment such as glycyrrhizin and magnesium isoglycirrhizinate was routinely given, and complications were treated symptomatically. The treatment lasted for 12 weeks. It was recommended that the medication be terminated in the case of disease progression or deterioration, severe adverse reactions, and hepatic decompensation (Child-Pugh grade C).

Observation indexes

The clinical efficacy was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1) according to the CT or MRI results. Complete response (CR): The lesions completely disappear after treatment for >1 month. Partial response (PR): The product of maximum diameter and maximum vertical diameter of lesion declines by >50% for >1 month. Stable disease (SD): The product of maximum diameter and maximum vertical diameter of lesion declines by <50% or increases by <25%, and there are no new lesions. Progressive disease (PD): The product of maximum diameter and maximum vertical diameter of lesion increases by ≥25%, or there are new lesions. Objective response rate (ORR) = (CR+PR)/total cases × 100%, and disease control rate (DCR) = (CR+PR+SD)/total cases × 100%.

The patients were re-examined once every 4-6 months, with clinical examination, general laboratory examination (hepatic and renal function, tumor markers and coagulation function), upper abdominal CT or MRI scan, and imaging examination, and they were followed up till death or lost to follow up. The levels of VEGF and bFGF were measured via enzyme-linked immunosorbent assay (ELISA) before treatment and 12 weeks after treatment. The level of serum alpha fetoprotein (AFP) was detected through the electrochemiluminescence method using the 411 electrochemiluminescence instrument and reagents (Roche, Basel, Switzerland). During chemotherapy, the adverse reactions were observed, evaluated and recorded based on the National Cancer Institute-Common Terminology Criteria Adverse Events (NCI-CTCAE) (Version 4.0), and were classified into grade I-IV. The patient overall survival (OS) was recorded, and the survival time was defined as the duration from initial diagnosis to death or May 31, 2019. The data of those lost to follow-up were deleted.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean±standard deviation, and t-test was performed for intergroup comparisons. Numerical data were expressed as rates (%), and x^2 test was performed for intergroup comparisons. P<0.05 suggested statistically significant difference. The survival curves were plotted using the Kaplan-Meier method, and log-rank

Table 2. Comparison of clinical efficacy of patients in the two groups

Parameters	*Sorafenib+TACE group (n=59)*	*TACE group (n=59)*	*p value*
CR	4	1	
PR	29	21	
SD	18	18	
PD	8	19	
ORR (%)	33 (55.9)	22 (37.3)	0.022
DCR (%)	51 (86.4)	40 (67.8)	0.027

TACE: Transcatheter arterial chemoembolization; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate

test was utilized to statistically assess significant differences in survival between the two groups. P<0.05 suggested statistically significant difference.

Results

Short-term efficacy evaluated

In the Sorafenib+TACE group, there were 4 cases of CR, 29 cases of PR, 18 cases of SD, and 8 cases of PD, and the ORR and DCR were 55.9% (33/59) and 86.4% (51/59). In the TACE group, there were 1 case of CR, 21 cases of PR, 18 cases of SD, and 19 cases of PD, and the ORR and DCR were 37.3% (22/59) and 67.8% (40/59). Both ORR and DCR in the Sorafenib+TACE group were significantly superior to those in the TACE group, and the differences were statistically significant (p=0.022, p=0.027) (Table 2).

Comparison of VEGF, bFGF and AFP levels between the two groups before and after treatment

Before and after treatment, the mean serum VEGF concentration was 478.13±70.92 pg/mL, 254.28±50.81 pg/mL in the Sorafenib+TACE group, and 465.80±84.69 pg/mL and 337.47±61.53 pg/mL in the TACE group. Before and after treatment, the mean serum bFGF concentration was 9.42±6.89 pg/mL and 4.49±4.26 pg/mL in the Sorafenib+TACE group, and 9.84±5.76 pg/mL and 6.26±5.15 pg/mL in the TACE group. Before and after treatment, the mean serum AFP concentration was 516.65±104.31 ng/mL and 292.86±78.49 ng/mL in the Sorafenib+TACE group, and 495.85±110.93 ng/mL and 361.18±69.58 ng/mL in the TACE group. It was revealed that the levels of serum VEGF, bFGF and AFP had no statistically significant differences between the two groups before treatment (p=0.393, p=0.720, p=0.296), and they were comparable. The levels of serum VEGF, bFGF and AFP declined significantly in both groups after treatment compared with those before treatment, showing statistically significant differences (p=0.013, p<0.001, p<0.001), while they were significantly lower in the Sorafenib+TACE group than in the TACE group after treatment (p<0.001, p=0.016, p<0.001) (Figure 1).

Adverse reactions and complications

The patients in both groups had adverse reactions in different grades during treatment, mainly

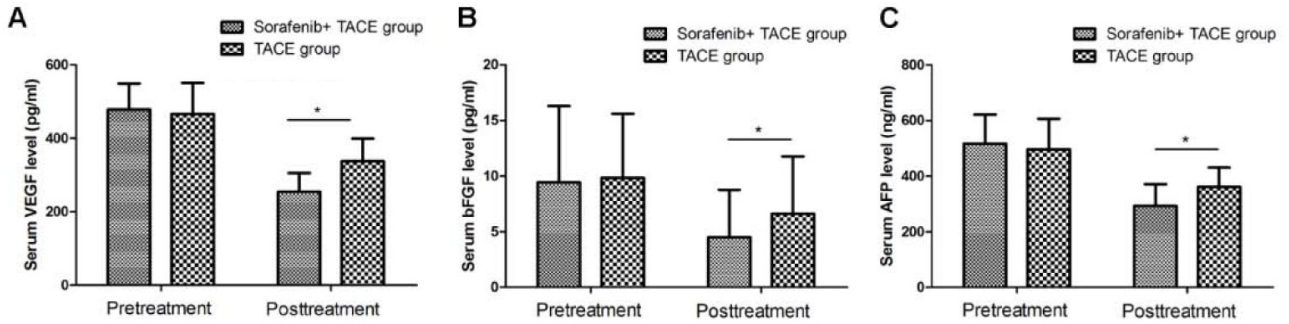

Figure 1. Comparison of serum VEGF, Bfgf, AFP levels of patients in the two studied groups. The difference of pretreatment serum VEGF **(A)**, bFGF **(B)** and AFP **(C)** levels of patients in the Sorafenib+TACE group and the TACE group had no statistical significance (p=0.393, p=0.720, p=0.296). After treatment, serum VEGF **(A)**, bFGF **(B)** and AFP **(C)** levels decreased dramatically in both groups. Posttreatment serum VEGF, bFGF and AFP levels of patients in the Sorafenib+TACE group was significantly lower than that of the TACE group (p<0.001, p=0.016, p<0.001).

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

	Sorafenib+TACE group (n=59) *n (%)*	*TACE group (n=59)* *n (%)*	*p value*
Bone marrow suppression	11 (18.6)	8 (13.6)	0.617
Fever	20 (33.9)	24 (40.7)	0.568
Rash	27 (45.8)	9 (15.3)	0.001
Nausea, vomiting	39 (66.1)	33 (55.9)	0.345
Diarrhea	26 (44.1)	10 (16.9)	0.002
Hepatalgia	12 (20.3)	15 (25.4)	0.662
Hypertension	14 (23.7)	2 (3.4)	0.002
Hand-foot syndrome	19 (32.2)	2 (3.4)	0.001

TACE: Transcatheter arterial chemoembolization

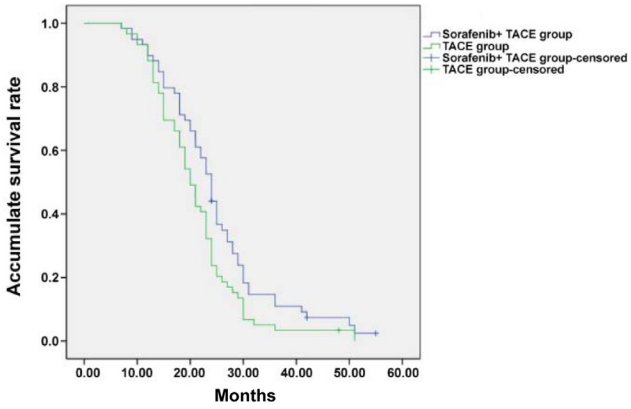

Figure 2. Kaplan-Meier survival curves of the studied patients. The overall survival rate of patients in the Sorafenib+TACE group was significantly higher than that of the TACE group (p=0.030).

including myelosuppression, fever, rash, gastrointestinal reactions, hepatalgia, hypertension and hand-foot syndrome, mostly of grade I-II, which were all improved after dose reduction and symptomatic treatment. No patients quit the treatment due to severe adverse reactions. In the two groups, there were 11 and 8 cases of myelosuppression, 20 and 24 cases of fever, 39 and 33 cases of nausea and vomiting, and 12 and 15 cases of hepatalgia, displaying no statistically significant differences (p>0.05). In the two groups, the incidence rate of rash was 45.8% (27/59) and 15.3% (9/59), that of diarrhea was 44.1% (26/59) and 16.9% (10/59), that of hypertension was 23.7% (14/59) and 3.4% (2/59), and that of hand-foot syndrome was 32.2% (19/59) and 3.4% (2/59), displaying that the incidence rates of rash, diarrhea, hypertension and hand-foot syndrome in the Sorafenib+TACE group were obviously higher than those in the TACE group (p<0.001, p=0.002, p=0.002, p<0.001) (Table 3).

Follow-up results of patient survival

All patients were followed up for 7-54 months with a median of 26.3 and 23.4 months, respectively. At the end of the follow-up, 2 patients in each group were lost to follow-up. The mean OS was 25.3±2.6 months in the Sorafenib+TACE group and 22.5±2.5 months in the TACE group. The 1-, 2- and 3-year survival rates were 71.9% (41/57), 42.1% (24/57) and 17.5% (10/57), respectively in the Sorafenib+TACE group, and 52.6% (30/57), 31.6% (18/57) and 8.8% (5/57), respectively in the TACE group. The Kaplan-Meier survival curves of patients are shown in Figure 2. The results of log-rank test showed that OS had a statistically significant difference between the two groups, remarkably longer in the Sorafenib+TACE group than that in the TACE group (p=0.030).

Discussion

In China, the morbidity rate of hepatocellular carcinoma ranks second after lung cancer among malignant tumors [10]. At present, the ideal treatment method for liver cancer is still radical surgical resection, but due to the insidious onset, no or non-obvious symptoms in the early stage, and rapid progression of liver cancer, most patients have been in the late stage or had distant metastasis when diagnosed, thus losing the opportunity of surgery. Therefore, TACE has become the preferred treatment for liver cancer patients, but it cannot achieve total necrosis of lesions, while it can promote the activation of VEGF and bFGF, and facilitate neovascularization, leading easily to tumor recurrence and metastasis [11,12]. Therefore, suppressing tumor angiogenesis on the basis of TACE may significantly improve the survival time of liver cancer patients and reduce the recurrence and metastasis.

Sorafenib is the first drug approved by the Food and Drug Administration for the first-line targeted therapy of patients with hepatocellular carcinoma. A large number of studies have shown that sorafenib, a multi-target antitumor drug, can inhibit tumor angiogenesis through blocking VEGF receptor and platelet-derived growth factor receptor, and also inhibit tumor cell proliferation through the Raf/MEK/ERK signaling pathway, exerting a dual antitumor effect [13,14]. With the application of Sorafenib in the treatment of liver cancer, TACE combined with Sorafenib has become a hot topic among researchers. Strebel et al [15] thought that the hypoxic environment caused by TACE induces increase of VEGF expression, and TACE combined with Sorafenib can effectively inhibit the formation of new blood vessels, reduce the tumor recurrence and metastasis, and improve the long-term efficacy on liver cancer. Chao et al [16] studied and showed that both median survival time and time to progression (TTP) of patients in BCLC stage B are remarkably benefited from TACE combined with Sorafenib. Moreover, Zhang et al [17] reported on the treatment of liver cancer patients with portal vein tumor thrombus using TACE+Sorafenib, and they found that TACE combined with Sorafenib can significantly improve the OS, ORR, DCR and TTP of patients.

In this study, both ORR and DCR in the Sorafenib+TACE group were significantly superior to those in the TACE group (p=0.022, p=0.027). The levels of serum VEGF, bFGF and AFP declined significantly in both groups after treatment compared with those before treatment (p=0.013, p<0.001, p<0.001), while they were evidently lower in the

Sorafenib+TACE group than those in the TACE group after treatment ($p<0.001$, $p=0.016$, $p<0.001$). It was observed that the incidence rates of diarrhea, hand-foot syndrome, hypertension and rash in the Sorafenib+TACE group (44.1%, 32.2%, 23.7% and 45.8%) were all obviously higher than those in the TACE group ($p<0.05$), consistent with the results in previous studies [18,19]. Although the incidence rate of adverse reactions in the combination therapy was higher than that in the TACE alone group, some studies have demonstrated that the occurrence of some adverse reactions may indicate a better response of tumor to treatment. It is reported in the literature that the total incidence rates of common adverse reactions of Sorafenib are as follows: 31-34% for rash, 30-43% for diarrhea, 19-30% for hand-foot syndrome, and 12-75% for hypertension. In this study, the incidence rates of toxic and side effects in the Sorafenib+TACE group had no significant increase compared with those in the TACE group alone, indicating that TACE combined with Sorafenib is safe and feasible for the treatment of advanced liver cancer [20].

The changes in the levels of VEGF and bFGF after TACE have been reported in many studies, but the time points selected and the increased time and change rule of VEGF and bFGF in blood are not the same, suggesting that Sorafenib combined with TACE and TACE alone have an inhibitory effect on the levels of serum VEGF and bFGF in liver cancer patients [21]. The results in this study manifested that the inhibitory effect on the levels of serum VEGF and bFGF in liver cancer patients in the Sorafenib+TACE group was better than that in the TACE group, demonstrating that the combination therapy suppresses the expressions of VEGF and bFGF, inhibits the tumor angiogenesis to some extent, and delays the construction of local collateral circulation of the tumor, thus prolonging the survival of liver cancer patients. Studies have confirmed that VEGF plays a leading role in angiogenesis of liver cancer, bFGF only synergizes with VEGF to promote angiogenesis, and the ischemia and hypoxia of liver cancer tissues after embolism may be the common cause of upregulation of VEGF and bFGF [22,23]. It has been found that bFGF can upregulate the expression of VEGF in culture experiments. However, the mechanism of the decline of expression levels of VEGF and bFGF after treatment using Sorafenib combined with TACE remains to be further studied.

There are still many limitations in this study. For example, the samples size was small, the follow-up content was not comprehensive enough, and the influence of different treatments on the quality of life of patients was not evaluated. In the future, further large-sample multicenter randomized controlled trials are needed to verify the conclusions made in this study, so as to offer a stronger basis to the selection of therapeutic regimen for such patients.

Conclusions

Compared with TACE alone, Sorafenib combined with TACE can significantly improve ORR and DCR, reduce significantly the levels of serum VEGF, bFGF and AFP, and prolong the survival of patients with advanced liver cancer, while the adverse reactions are tolerable, so it is worthy of clinical popularization and application.

Conflict of interests

The authors declare no conflict of interests.

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