

Transarterial Chemoembolization Combined with Sorafenib in Patients with BCLC Stage C Hepatocellular Carcinoma

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

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Purpose: Transcatheter arterial chemoembolization (TACE) and targeted therapy have become common methods in the treatment of advanced hepatocellular carcinoma (HCC). The purpose of this study was to evaluate the safety and efficacy of TACE combined with sorafenib (TACE-sorafenib) and TACE alone for the treatment of Barcelona clinical stage C HCC.

Methods: The clinical data of 75 patients with BCLC stage C HCC who received TACE-sorafenib or TACE as the initial treatment were retrospectively analyzed. Tumor response, time to progression (TTP), overall survival (OS), and adverse events were compared at 1 month after surgery in the two groups.

Results: One month after treatment, the disease control rate in the TACE-sorafenib group was higher than that in the TACE group alone (82.76% and 57.50%, respectively, $P = 0.018$). The median values of TTP and OS in the TACE-sorafenib group were longer than those in the TACE group (TTP was 7.6 and 3.4 months, respectively, $P = 0.002$; OS was 13.6 and 6.3 months, respectively, $P = 0.041$). The cumulative survival time at 3 months, 6 months, and 1 year was higher in the TACE-sorafenib group than in the TACE group (83.5%, 71.2%, 45.7% vs 57.4%, 40.6%, 21.2%). Sorafenib-related side effects such as hypertension, hand-foot syndrome, and oral ulcers were more common than those in the TACE group alone ($P < 0.05$).

Conclusion: Compared with TACE treatment alone, TACE combined with sorafenib in BCLC-C stage HCC significantly improved disease control rate, TTP, and OS, and no significant increase in adverse reactions was observed.

Keywords: hepatocellular carcinoma, TACE, sorafenib, survival

Introduction

Hepatocellular carcinoma (HCC) is one of the common malignant tumors with high mortality in the digestive system.¹ It has the characteristics of occult disease, high malignancy, fast growth, wide metastasis, short natural course and high recurrence rate.^{2,3} Surgical resection is the first choice for the treatment of early HCC, but most patients have advanced cancer when diagnosed, and the effect of resection is poor.⁴ Meanwhile, the sensitivity of HCC to the radiotherapy and chemotherapy is also unsatisfactory.⁵ Transcatheter arterial chemoembolization (TACE) is mostly used in patients with advanced HCC who do not meet the condition of radical resection.^{6,7} TACE alone is often difficult to obtain a satisfactory curative effect, especially in the patients with advanced HCC. The reasons are partially contributed to the increase of vascular endothelial growth factor induced by the heightening of hypoxia after tumor necrosis, thereby increasing the formation of tumor

vessels.^{8,9} Therefore, it is essential to give an anti-angiogenesis for patients who accepted TACE treatment for improving clinical efficacy, reducing tumor recurrence and metastasis, and prolonging the survival. Sorafenib is an oral multikinase inhibitor, which can directly inhibit the Ras/Raf/MEK/ERK signaling pathway to inhibit the proliferation of tumor cells, and can also inhibit the activity of related receptors related to neovascularization. It can inhibit the secretion of VEGF and other cellular inflammatory factors, thereby blocking the formation of tumor new blood vessels and inhibiting the growth of tumors. According to the criteria for the diagnosis and treatment of Barcelona Clinic Liver Cancer system, patients with HCC in BCLC stage B (Child-Pugh grade A to B) are preferred for TACE therapy, and patients in stage C are treated with sorafenib.¹⁰ While if TACE in combine with sorafenib can obtain an improved effect for patients with BCLC stage C HCC is uncertain. This study conducts a retrospective analysis to evaluate the effect of TACE combined with sorafenib.

Materials and Methods

This study was carried out in accordance with the principles set out in the declaration of Helsinki in 1964. Approved by the ethics committee of the First Affiliated Hospital of the University of Science and Technology of China, through the retrospective study design and analysis of clinical data, the ethics committee of the First Affiliated Hospital of the University of Science and Technology of China formally gave up informed consent. All patient information is confidential.

Study Population

A total of 307 patients with stage BCLC-C HCC treated in the First Affiliated Hospital of the University of Science and Technology of China from January 2010 to December 2018 were collected. The inclusion criteria were as follows: (1)the diagnostic standards being in line with the criteria endorsed by the American Association for the Study of Liver Diseases;² (2)stage C HCC based on BCLC staging criteria;¹¹ (3)Child-pugh classification of A or B; (4)Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; (5)white blood cell count $\geq 2000/\mu\text{L}$, hemoglobin ≥ 8.0 g/dL, and platelet count $\geq 6.0 \times 10^4/\mu\text{L}$; (6)tumors size less than 70% of the whole liver volume; Exclusion criteria included: patients who had undergone systemic chemotherapy, targeted therapy or radiofrequency ablation (RFA) previously; (2)patients with other primary malignancies, or other concurrent serious

medical conditions;(3)patients who had contraindications to TACE treatment; (4)severe coagulopathy; This study finally included 84 patients with stage BCLC-C liver cancer. They were divided into TACE group (n = 40) and combination group (n = 35, TACE plus sorafenib) according to the difference of therapeutic modalities (Figure 1).

Treatment Methods

Patients in both groups were treated with modified Seldinger method for TACE. The angiographies of celiac, hepatic, inferior phrenic arteries, and superior mesenteric were conducted to identify the feeding arteries of tumor. A 2.8 Fr micro-catheter (ProgreatTM, Terumo, Tokyo, Japan) was inserted to feeding arteries of tumor. Oxaliplatin (100–200 mg) and/or fluorouracil glycosides (500–1000 mg) were infused followed by epirubicin (30–60 mg) mixed with 5–25 mL of iodized oil under fluoroscopic monitoring, the dose of chemotherapeutic drugs and super emulsified lipiodol depends on the number, size, and blood supply of tumor lesions.

Patients in the combination group received oral sorafenib (Bayer Pharmaceuticals, 20,131,118, 0.2g/tablet) on the 4th day following TACE treatment. The dose was 400 mg, BID. If the intolerable adverse reaction occurred, the dose was adjusted to 200 mg, BID, or stop taking Sorafenib after symptom relief for about 2 weeks, usually for at least 3 months or until the disease progresses. During medication, liver disease progressed to Child Pugh Grade C or was lost to follow-up, and drug resistance was discontinued. If new lesions and residual lesions appear at intervals of more than 1 month after re-examination of imaging, both groups can be treated with TACE again.

Observation Indicators

(1)Efficacy Evaluation After 1 month of treatment, the modified mRECIST standard¹² was used to evaluate the efficacy. The efficacy evaluation criteria are as follows: Complete Response (CR): disappearance of intra-tumor arterial enhancement in all target lesions; Partial Response (PR): The sum of all the diameters of target lesion size or enhanced lesions at least 30% is reduced; Stable Disease (SD): the minimum diameter of the target lesion has neither reached the PR nor increased the diameter requirements of the disease progression; Progression Disease (PD): tumor size (The sum of the diameters of all enhanced lesions and the largest diameter of the lesions) increased by at least 20%, or new lesions appeared. (2) Adverse Reactions Refer to the

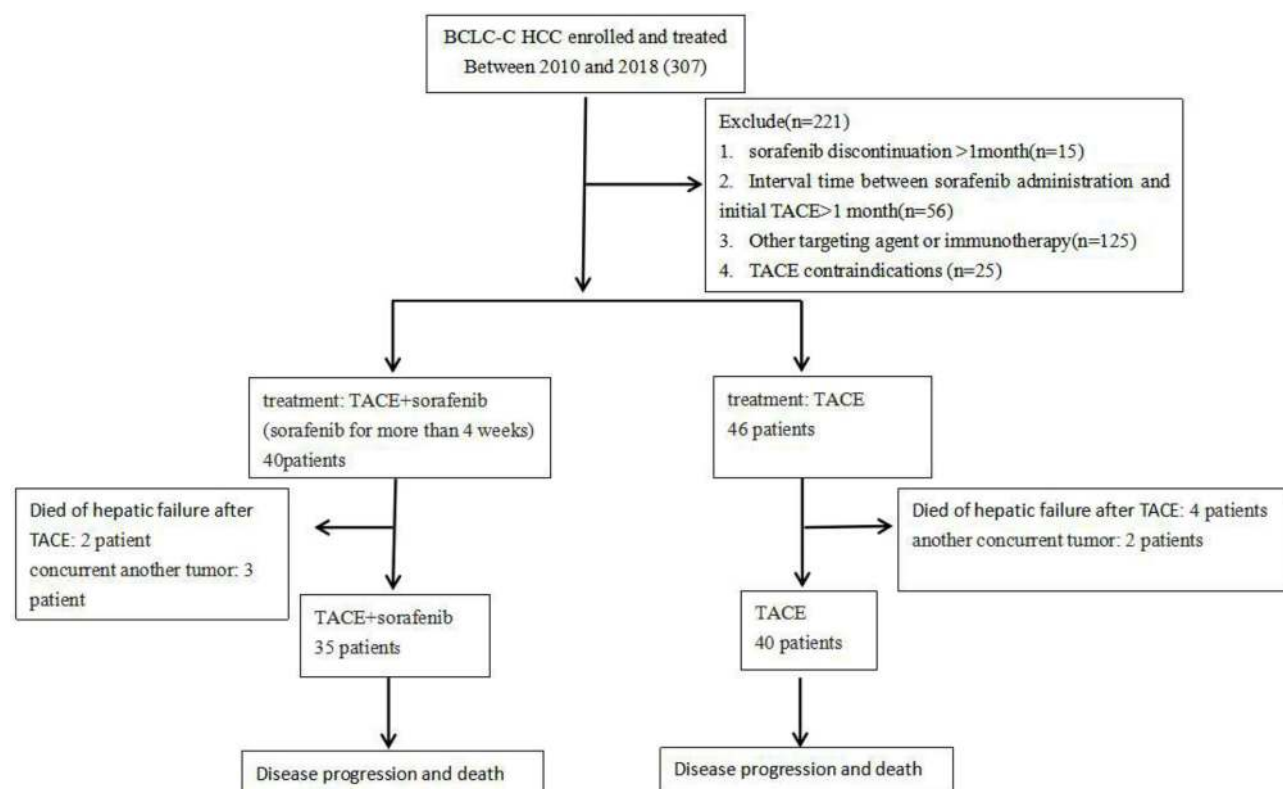


Figure 1 Flow diagram illustrating the treatment process.

National Cancer Institute's Common Adverse Reaction Rating Standard 3.0¹³ to observe the occurrence of adverse reactions in the two groups. (3) Survival Time Calculate the median overall survival (OS) of the two groups. OS is defined as the time from the first TACE after surgery to death or termination of follow-up.

Study Endpoint

The primary endpoint was overall survival or last follow-up (December 31, 2019). For survival analysis, a follow-up of at least 3 months was considered mandatory. The final date of the follow-up was from an outpatient visit or telephone interview. The secondary endpoint was tumor response as defined by the mRECIST criteria and treatment-related adverse events.

Statistical Methods

Statistical analysis was performed using SPSS20.0 software. Measurement data were expressed as $\pm s$, using two independent sample t tests; count data were taken as examples, using χ^2 test; Kaplan-Meier method was used for survival analysis, and comparison was performed by Log rank test. $P < 0.05$ was considered statistically significant.

Results

Comparison of Baseline Data

There were no significant differences in baseline data ($P > 0.05$) in age, gender, Child-Pugh classification, preoperative AFP, tumor size, number of tumors, history of hepatitis B, and presence or absence of metastasis ($P > 0.05$) (Table 1).

Tumor Response

After 1 month of treatment, the tumor response was evaluated according to mRECIST standard based on the imaging follow-up results. It was found that the disease control rate of the combined group was significantly better than that of TACE ($P = 0.018$), suggesting that sorafenib can significantly improve the efficacy of TACE (Table 2).

Adverse Reactions

The adverse reactions in the two groups were mainly gastrointestinal reactions, bone marrow suppression, skin reactions, and abnormal liver function. In 8 patients, the dose of sorafenib was reduced to 200mg twice a day due to intolerance. No serious adverse reactions occurred. After symptomatic treatment, the symptoms were alleviated significantly and had no

Table 1 Baseline Characteristics of Two Groups' Patients

	TACE+Sorafenib(n=35)	TACE(n=40)	P
Age (years), median (range)	68.24 (35–88)	56 (35–85)	0.33
Sex (M/F)	30/5	32/8	0.51
Tumor size (cm), median (range)	6.9 (1.6–12)	7.4 (2.1–11.7)	0.28
Tumor number (single/multiple)	18/17	27/13	0.15
PVTT(Yes/No)	24/11	28/12	0.89
HBsAg (Yes/No)	31/4	34/6	0.64
AFP (≤ 400 ng/L/ >400 ng/L)	12/23	21/19	0.11
ECOG (0–1/ >1)	32/3	34/6	0.39
Child-Pugh class (A/B)	23/12	24/16	0.61
Extrahepatic metastasis(Yes/No)	11/24	18/22	0.23
Number of TACE (≤ 3 / >3)	28/7	26/14	0.15
Duration of Sorafenib treatment, (days)	439.4	-	-

Abbreviations: TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombus; HBsAg, hepatitis B surface antigen; AFP, alpha fetoprotein; ECOG, Eastern Cooperative Oncology Group.

Table 3 Treatment-Related AEs in Patients in Two Groups[n(%)]

Adverse Events	TACE+Sorafenib(n=35)	TACE(n=40)	χ^2	P
Nausea	21(60%)	22(55%)	0.19	0.66
Diarrhea	17(48.6%)	21(52.5%)	0.12	0.73
Leukopenia	20(57%)	16(40%)	2.19	0.14
Fever	24(69%)	28(70%)	0.02	0.89
Liver function lesion	6(17.1%)	9(22.5%)	0.33	0.56
Oral Mucositis	25(71.4%)	2(5%)	35.75	<0.001
Fatigue	24(68.6%)	23(57.5%)	0.98	0.32
Alopecia	13(37.1%)	10(25%)	1.29	0.25
Hand-foot skin reaction	27(77.1%)	1(2.5%)	44.45	<0.001
Hypertension	12(34.3%)	2(5%)	10.54	0.001

Table 2 Summary of Tumor Response[n(%)]

	CR	PR	SD	PD	ORR (%)	DCR (%)
TACE+Sorafenib	3(8.57%)	12(34.28%)	14(40%)	6(17.14%)	15(42.85%)	29(82.86%)
TACE	2(5%)	10(25%)	11(27.5%)	17(42.5%)	12(30.00%)	23(57.50%)
χ^2					1.34	5.64
P					0.25	0.018

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; TACE, transarterial chemoembolization.

effect on subsequent treatment. The incidence of skin reactions, oral mucositis and hypertension in the experimental group was significantly higher than that in the control group ($P < 0.01$) There was no significant difference in the incidence of nausea and vomiting, abdominal pain and diarrhea, decreased leukocyte, and abnormal liver function in the two groups ($P > 0.05$) (Table 3).

TTP and OS

Two groups of patients were followed up and found that the half-year, one-year, and two-year survival rates of patients in the TACE group were 57.4%, 40.6%, and 21.2%, respectively; the survival rates of patients in the combined group were 83.5%, 71.2%, and 45.7%. The overall survival time of patients in the TACE group was

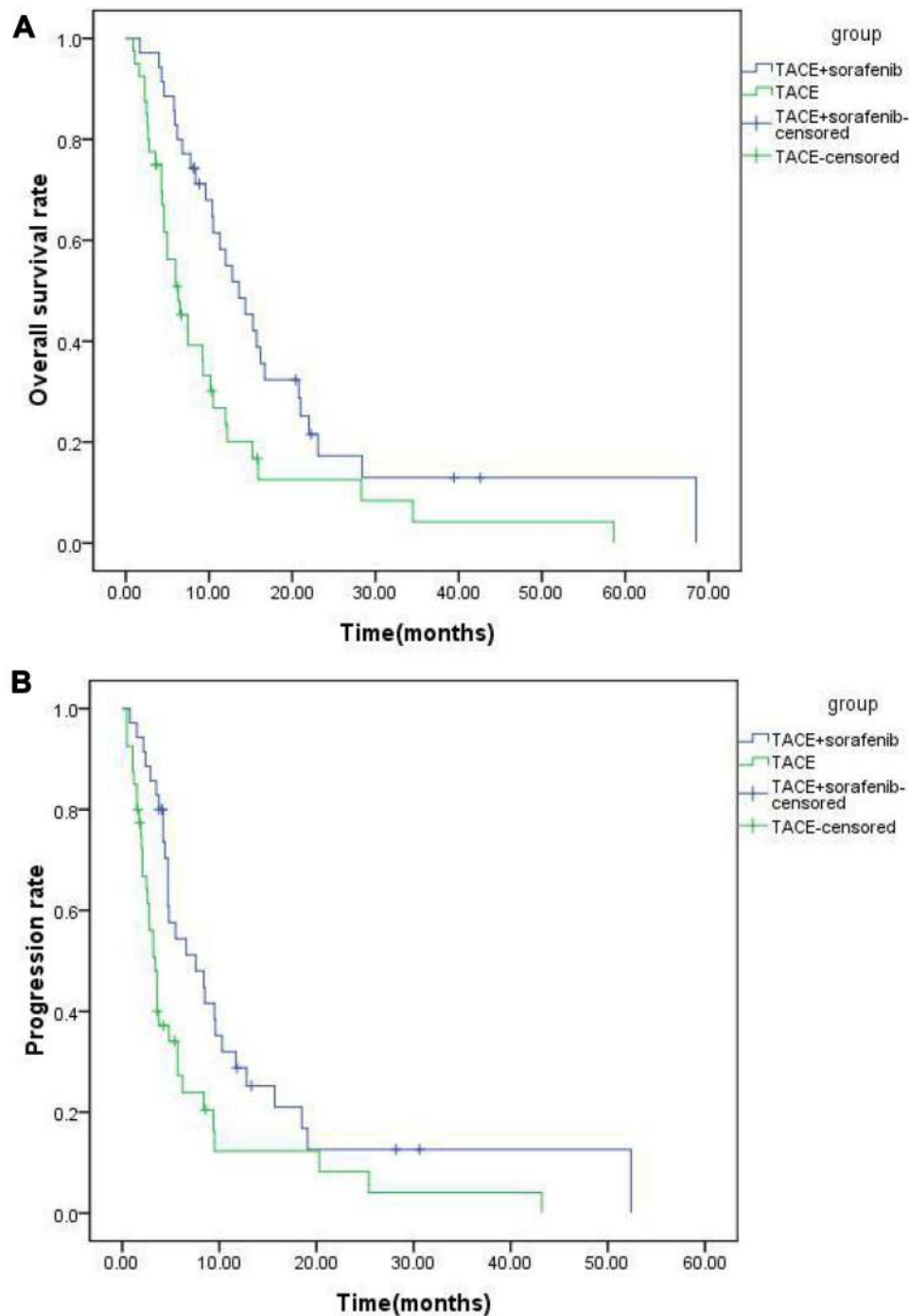


Figure 2 (A) Kaplan–Meier survival curves for comparison of OS between TACE + sorafenib group and TACE group ($P=0.016$). (B) Kaplan–Meier survival curves for comparison of TTP between TACE + sorafenib group and TACE group ($P=0.042$).

6.5 months, and the time to progression was 3.4 months. The total survival time of patients in the combination group was 13.6 months, the time to progression was 7.6 months, and the total survival time of the combination group ($P = 0.016$, Figure 2A) and time to progression ($P=0.042$, Figure 2B) were significantly better than the TACE group.

Discussion

TACE plays an important role in the treatment of unresectable advanced HCC. Previous studies have confirmed that TACE can significantly prolong the median survival time of patients with advanced HCC.^{14,15} However, the individual differences among patients receiving TACE are large, and the recurrence

rate is high. The recurrence rate within 6 months is as high as 29%.¹⁶ The curative effect is an important factor restricting its widespread clinical application. Sorafenib, as a commonly used molecular targeted drug, has also shown great application potential in the treatment of advanced HCC. Related studies have confirmed that sorafenib can prolong the overall survival of patients with advanced HCC outstanding drug tolerance.^{17,18} Several international authoritative guidelines recommend sorafenib as the standard treatment for advanced hepatocellular carcinoma, and point out that sorafenib inhibits tumor cell proliferation and inhibits tumor angiogenesis. Early application of sorafenib after palliative surgery may delay tumor recurrence. However, domestic studies mostly focus on patients with BCLC stage B. The overall treatment effect for patients with BCLC stage C is still unclear. Even for patients with BCLC stage B, there is also some controversy in clinical studies. Domestic studies have shown that TACE combined with sorafenib in the treatment of BCLC Phase B, compared with TACE alone, has not shown significant advantages.¹⁹ This study explored the overall efficacy of TACE combined with sorafenib in patients with BCLC stage C HCC.

Molecular targeted drugs are the current research hotspots in tumor therapy and one of the new directions in the treatment of hepatocellular carcinoma. Compared with traditional anti-tumor drugs, it has the advantages of higher pertinence, specificity and less toxic and side effects. The pathogenesis of liver cancer involves numerous signaling pathways. Sorafenib is a small molecule multi-targeted oral multikinase inhibitor. It inhibits Raf/MEK/ERK signaling pathways by inhibiting Raf kinases on the one hand, and inhibits VEGFR-2, VEGFR-3, and PDGFR on the other β , FLT-3, c-Kit receptors to inhibit HCC cell proliferation, prevent tumor cell angiogenesis, and effectively induce HCC ectopic planting apoptosis.^{20,21} It is currently the only targeted therapeutic drug that has obtained evidence-based medical evidence that can prolong the survival of hepatocellular carcinoma. Both the SHARP study in Europe²² and the Oriental study in Asian populations²⁰ have confirmed that patients taking sorafenib have longer disease progression times and overall survival times than patients on supportive care.

Although TACE can treat tumor from both sides of arterial chemotherapy and embolization, TACE also has its shortcomings, mainly because in addition to the main hepatic artery blood supply, liver cancer also receives a portion of the blood supply from the portal vein, which leads to the opening of the hepatic artery-portal communication branch after embolization, leading to incomplete embolism; The effect of TACE on

hepatocellular carcinoma with poor blood supply is poor.²³ In addition, most of the non-necrotic liver cancer tumor cells after TACE are in a proliferative active state. Due to tumor vessel embolism, these tumor cells are in an ischemic and hypoxic state, which can promote some angiogenic factors such as VEGF, serum insulin-like Increased secretion of growth factor-2 (IGF-2), etc., promotes the formation of tumor neovascularization, and the neovascularization and other blood vessels in the liver form a collateral circulation, which also increases the chance of recurrence and metastasis, which affects long-term efficacy.²⁴ If an anti-angiogenic drug can be given after liver cancer TACE, it may reduce the chance of recurrence and metastasis in patients with hepatocellular carcinoma, thereby prolonging the survival of patients. TACE and sorafenib targeted therapy theoretically have complementary antitumor effects. Therefore, the combined application of the two in the treatment of primary liver cancer is a hot spot in clinical research. Wei et al²⁵ believe that sorafenib can inhibit tumor cell proliferation and anti-angiogenesis through multi-target inhibition and dual-channel inhibition mechanisms, and complement TACE. Park et al compared the clinical effects of TACE combined with sorafenib and the two alone in treating primary liver cancer.²⁶ The results showed that TACE combined with sorafenib had a more significant effect than the two alone.

The data of this study showed that there was no statistically significant difference in the incidence of adverse reactions such as fever, leukopenia, liver damage, and gastrointestinal reactions in patients with TACE combined with sorafenib and those with TACE alone during treatment. There are differences in mucositis, hand-foot-mouth disease, and hypertension, and most of the adverse reactions occur 2 to 4 weeks after medication, and gradually relieve after treatment. This shows that the incidence of adverse reactions in patients with liver cancer treated only by TACE and TACE combined with sorafenib was similar, and the addition of sorafenib did not increase the incidence of adverse reactions. Its adverse reactions mostly occurred 2 to 4 weeks after treatment, and gradually relieved after treatment. This shows that TACE in combination with sorafenib is safe in treating primary liver cancer. Patients with liver cancer were treated with sorafenib after TACE. Not only the short-term efficacy was higher than that of single TACE therapy, but the long-term efficacy was higher than that of TACE group. The median survival at one month, six months, and one year was statistically significant compared with patients in the TACE group, which is consistent with the efficacy of Peng et al²⁷ for the recurrence of postoperative

recurrence of sorafenib combined with TACE in the treatment of advanced liver cancer.

This study also has certain shortcomings. First, the number of patients enrolled is small, and related cases will continue to be included in subsequent studies for further research. Second, factors that affect the survival time of patients with BCLC stage C are not analyzed. Rather, it simply analyzes the overall disease progression time and survival time, and will further study on the premise that the number of subsequent cases increases.

In summary, patients with BCLC stage C treated with sorafenib combined with TACE have a gain effect, can significantly benefit patients, and significantly prolong the overall survival time of these patients.

Funding

This work was supported by the Natural Science Project of Anhui Province of China (No. 1808085MH254).

Disclosure

The authors report no conflicts of interest for this work.

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