JBUON 2018; 23(1): 193-199
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Sunitinib versus sorafenib plus transarterial chemoembolization for inoperable hepatocellular carcinoma patients

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Summary

Purpose: *To compare sunitinib vs sorafenib plus transarterial chemoembolization (TACE) for inoperable hepatocellular carcinoma (HCC) patients.*

Methods: *From January 2010 to December 2016, 104 patients with inoperable stage III HCC were included and randomly divided into two groups. Patients in the sunitinib+TACE (SU+TACE) group received sunitinib orally 37.5 mg daily, while patients in the sorafenib+TACE (SO+TACE) group received sorafenib 400 mg twice daily. The two groups were given sunitinib or sorafenib on an interrupted schedule, with a 4–7 days interval before or after TACE sessions. TACE treatment was repeated every 6–8 weeks. Patients were treated for about 4–6 cycles until the occurrence of toxicity or patient refusal, or progressive disease.*

Results: *The median overall survival (OS) and the median progression-free survival (PFS) in the SO+TACE group were significantly higher than that in the SU+TACE (OS: p=0.017; PFS: p=0.036, respectively). The rates of response and disease control were higher in the SO+TACE group (58%, 79%, respectively) compared to the SU+TACE group (37%, 66%, respectively), although without statistical significance. Regarding the toxicities, we found higher rates of hand-foot skin reaction (HFSR) in the SO+TACE group, while frequent occurrence of thrombocytopenia and neutropenia in the SU+TACE group.*

Conclusions: *The SO+TACE regimen was more effective and well tolerated in patients with unresectable stage III HCC compared to the SU+TACE regimen. The SO+TACE regimen may be a better alternative to the current standard regimens.*

Key words: *hepatocellular carcinoma, sunitinib, sorafenib, transarterial chemoembolization*

Introduction

Hepatocellular carcinoma (HCC) is a highly prevalent malignant disease, particularly in China and some other Asian parts [1,2]. Despite the development in the diagnosis and treatment, HCC remains the third leading cause of cancer related mortality worldwide [3]. Chemotherapy is one of the three commonly used methods for HCC treatment, especially for those who are not suitable for surgery. But the current chemotherapy of HCC is far from satisfactory due to its drug resistance [4]. Thus, for most patients with HCC, more effective cancer chemotherapy is urgently needed [5].

TACE is a important method to treat non-surgical HCC patients with intermediate stage that was defined as Barcelona Clinic Liver Cancer (BCLC) stage B [6]. A previous clinical study has reported that complete/partial tumor responses after treatment of TACE could increase the survival rate [7]. TACE delivers higher concentration of drugs to tumor than oral chemotherapy and decreases systemic exposure [8,9]. TACE has also been found to prolong survival and significantly delay the course of vascular invasion and tumor progression, achieving 16-61% objective respons-

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Received: 31/10/2017; Accepted: 19/11/2017

es in HCC patients [10]. Moreover, some studies showed that TACE could be carried out effectively and safely and might improve survival in selected HCC patients, including those with extra hepatic metastasis and those with tumor invasion into the main trunk of the portal vein [11,12]. Additionally, Pinter et al. [13] have reported that TACE achieved comparable tolerability and survival outcome as sorafenib in advanced-stage HCC patients and equally preserved their liver function.

Despite the improvement in recent surveillance programs, a large number of HCC patients are also diagnosed at advanced BCLC stage C, with distant metastasis or vascular invasion, for which systemic chemotherapy with sorafenib is currently considered as a standard treatment [6]. Concidering that there is no other proven effective therapy available for advanced HCC patients, new treatments are in urging need. Sunitinib is multitargeted tyrosine kinase inhibitor [14,15] and its antitumor activities have been reported in 2 different trials of advanced HCC [16,17]. Thus, it is intersting to explore if sunitinib is as same effective as sorafenib for treating inoperable advanced HCC.

We herein conducted a randomized controlled pilot study to investigate the efficacy and feasibility of sorafenib plus TACE for treating inoperable stage III HCC patients compared to sunitinib plus TACE. Our aim was to determine if sorafenib plus TACE is a beneficial alternative regimen to sunitinib plus TACE.

Methods

Patient selection

In this trial selected were 104 patients diagnosed with unresectable stage III HCC and divided randomly into two groups. One group was treated with SU+TACE, while the second one was treated with SO+TACE at the Nanjing Cancer Center from January 2010 to December 2016. The diagnosis was confirmed according to the criteria of American Association for the Study of Liver Diseases (AASLD). Detailed examinations were performed before therapy administration in all the included patients, such as abdominal, chest and brain CT, and also blood tests and serum biochemistry. Each patient provided written informed consent before the study entry. This study was approved by the ethics committee of Wujin Hospital Affiliated to Jiangsu University.

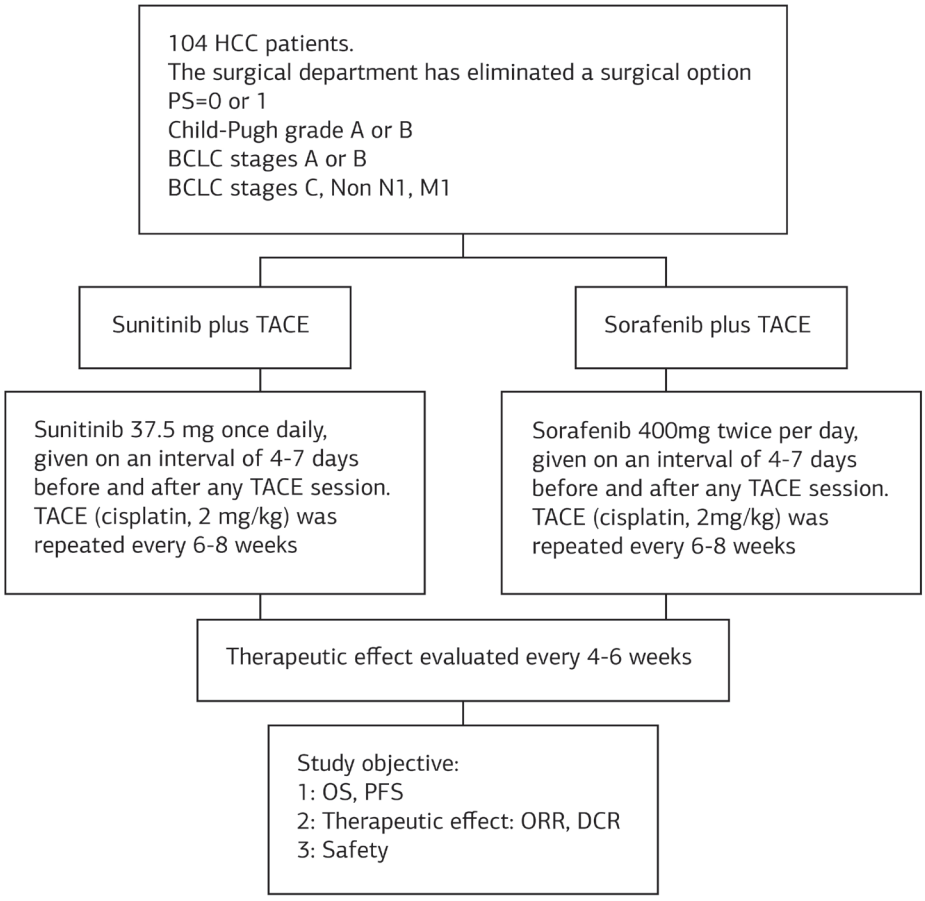

Figure 1. Flow chart of the treatment plan. HCC: hepatocellular carcinoma, OS: overall survival, PFS: progression free survival, ORR: objective response rate, DCR: disease control rate, TACE: transarterial chemoembolization, BCLC: Barcelona Clinic Liver Cancer staging.

The inclusion criteria in this study were as follows: age ≤75 years, ECOG performance status (PS) ≤1, Child-Pugh grade A or B, with enough reserve function in kidney, bone marrow and liver, BCLC staging of hepatic lymph nodes metastasis (N1) and distant metastasis (M1), except for patients in stage A, B or C. The exclusion criteria were: other histological kinds of malignancies, tumor occupying more than 70% of the liver volume, having been treated with any other prior antitumor drugs, and some serious complications, including active infection, severe renal and respiratory failure, severe heart disease, and poorly controlled diabetes mellitus / hypertension.

Treatment schedule

All included HCC patients were randomly divided into two groups to receive SU+TACE or SO+TACE therapy. As shown in Figure 1, patients in the SU+TACE group were administered orally 37.5 mg sunitinib once daily at the start of the trial and 12.5 mg incremental dose reduction was allowed to tolerate toxicities. Patients in the SO+TACE group were administered orally sorafenib 400 mg twice a day, with dose-reduction allowed to tolerate toxicities. The two combined groups were given sunitinib or sorafenib on an interrupted schedule, with a 4–7 days interval before or after TACE sessions. TACE was repeated every 6–8 weeks if residual viable tumor tissues were evident on sequential dynamic liver CT without deterioration of the liver function. Patients were treated as long as development of unacceptable toxicity or patient refusal, or progressive disease occurred. Dose modification was allowed in case of non tolerable toxicities. Patients were put on follow-up until death or study termination.

The TACE procedure was performed in our institution. Briefly, both common hepatic arteriography and superior mesenteric arteriography were carried out to evaluate portal vein patency, overall anatomy, and tumor burden. Then, without embolic particle administration, cisplatin 2 mg/kg was infused into the lobar hepatic artery for 15 min. With a microcatheter to selectively finish the catheterization of the hepatic feeding arteries, a 2-20 mL emulsion containing cisplatin and iodized-oil in a 1:1 ratio was infused into the feeding artery. The feeding artery was embolized subsequently with 1-mm diameter absorbable gelatin sponge particle until arterial flow stasis was obtained.

Evaluation of toxicity and response

During the treatment period, complete blood counts, serum biochemistry and abdominal CT were carried out every week. Response was assessed based on the Response Evaluation Criteria in Solid Tumor (RECIST) [18]. Toxicities of any treatment for all the patients were assessed and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0 [19].

Statistics

SPSS 20.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Quantitative data were expressed as mean ± standard deviation. Comparison between groups was done using One-way ANOVA test followed by *post hoc* test (Least Significant Difference). Percents were used to express the enumeration data and chi-square test was used for data analysis. To test grade data the non-parametric total rank of independent samples was used. OS was defined as the time from the beginning of chemotherapy until the patients' death or last seen. Surviving patients were censored on the day they were found alive at the last follow-up. PFS was defined as the time from the beginning of chemotherapy until patients' death, disease progression or follow-up completion. Patients that had not progressed when the treatment suspended continued to be evaluated before progression was confirmed. OS and PFS rates were evaluated with the Kaplan-Meier method and compared with the log-rank test. A p value ≤0.05 was considered as statistically significant.

Results

Patient characteristics

Baseline patient characteristics are shown in Table 1. No statistical difference was found between the two treated groups concerning their age, gender, ascites, hepatitis, ECOG PS, BCLC staging, blood vessel invasion, liver function, Child-Pugh and the follow-up time.

Toxicity

The adverse events observed in all 104 patients are listed in Table 2. Regarding grade 3 or higher toxicities of chemotherapy, we found higher rates of thrombocytopenia and neutropenia in the SU+TACE group (thrombocytopenia, p=0.017; neutropenia, p=0.039). Grade 3 or more severe HFSR was noticed in the SO+TACE group than in the SU+TACE group (HFSR, p=0.030). There were no significant differences concerning other toxicities between the two therapy regimens. Besides, no treatment-related death was encountered in both groups.

The median cycles of chemotherapy were 3.6 (range 1-6) in the SU+TACE treated group and 3.7 (range 1-6) in the SO+TACE treated group (p=0.663).

Comparison of treatment response

Among the 51 patients in the SU+TACE group, 15, 16, 19 and 1 showed stable disease (SD), progressive disease (PD), complete response (CR)/partial response (PR) and not evaluated (NE), respectively. As shown in Table 3, the response rate to SU+TACE treatment was 37%, and the rate of disease control 66%. On the other hand, among the 53 patients in the SO+TACE treated group, 11, 11 and 31 patients showed a PD, SD and CR/PR, respectively. The response rate to SO+TACE treatment was 58% and the disease control rate was up to 79%.

Table 1. Baseline patient characteristics

Characteristics	*Sunitinib plus TACE n=51 n (%)*	*Sorafenib plus TACE n=53 n (%)*	*p value*
Gender			0.526
Male	42 (82.4)	41 (77.4)	
Female	9 (17.6)	12 (22.6)	
Age, years			0.323
Median	60	62	
Range	41-71	45-75	
Hepatitis condition			0.906
Hepatitis B	39 (76.5)	42 (79.2)	
Hepatitis C	8 (15.7)	6 (11.3)	
Hepatitis B + hepatitis C	2 (3.9)	2 (3.8)	
Non-hepatitis	2 (3.9)	3 (5.7)	
ECOG performance status			0.323
0	29 (56.9)	25 (47.2)	
1	22 (43.1)	28 (52.8)	
Ascites			0.884
Yes	10 (19.6)	11 (20.8)	
No	41 (80.4)	42 (79.2)	
Child-Pugh liver function			0.497
Grade A	48 (94.1)	48 (90.6)	
Grade B	3 (5.9)	5 (9.4)	
Diameter of tumor target lesion, cm			0.991
≤10	27 (52.9)	28 (52.8)	
>10	24 (47.1)	25 (47.2)	
Number of tumors			0.406
>3	19 (37.3)	24 (45.3)	
≤3	32 (62.7)	29 (54.7)	
Blood vessel invasion			0.358
No	37 (72.5)	34 (64.2)	
Yes	14 (27.5)	19 (35.8)	
BCLC stage			0.595
Stage A	6(11.8)	5 (9.4)	
Stage B	11 (21.6)	16 (30.2)	
Stage C	34 (66.7)	32 (60.4)	
Relapse after surgical resection	5 (9.8)	7 (13.2)	0.587
Follow-up time, median (range) months	8.3 (1.3-15.2)	9.2 (2.8-14.6)	0.215

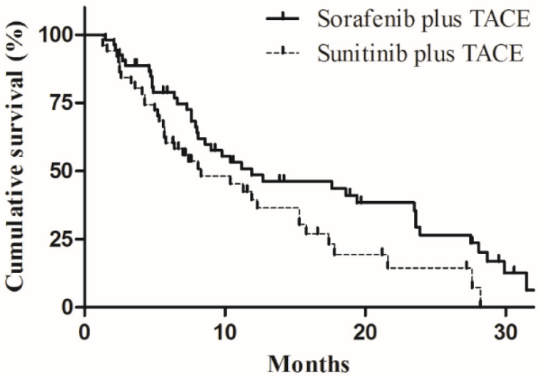

Figure 2. Kaplan-Meier analysis for overall survival of patients treated with sunitinib + TACE and sorafenib + TACE therapy regimens (log rank, p=0.017).

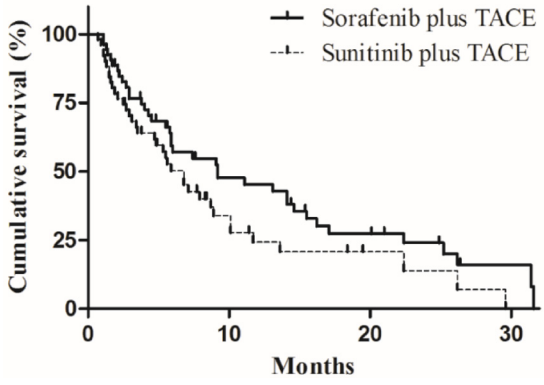

Figure 3. Kaplan-Meier analysis for progression-free survival of patients treated with sunitinib+TACE and sorafenib+TACE therapy regimens (log rank, p=0.036).

The response and disease control rates were higher in the SO+TACE group compared to SU+TACE group, although without statistical significance (response rate, p=0.146; disease control rate, p=0.116).

Comparison of survival

As shown in Figures 2 and 3, the median OS and PFS were 9.2 months (range 1.3-28.2) and 6.9 months (range 0.7-29.6) in the SU+TACE treated group. On the other hand, the median OS and PFS were 13.2 months (range 1.5-32.9) and 10.2 months (range 1.1-31.6) in the SO+TACE treated group. The results indicated that the median OS and PFS in the SO+TACE treated group were both significantly higher than that in the SU+TACE treated group (OS: p=0.017; PFS: p=0.036).

Table 2. Toxicity grades of the two combination therapies

Toxicity	*Sunitinib plus TACE n=51*						*Sorafenib plus TACE n=53*					
	Gr1	*Gr2*	*Gr3*	*Gr4*	*≥Gr3*	*All*	*Gr1*	*Gr2*	*Gr3*	*Gr4*	*≥Gr3*	*All*
Abdominal pain NOS	10	19	5	1	12	69	21	13	4	0	8	72
Thrombocytopenia	23	13	6	5	22	92	18	19	3	0	6	75
Neutropenia	15	13	5	3	16	71	9	7	2	0	4	34
Diarrhea	5	14	2	0	4	41	13	10	1	0	2	45
HFSR	18	6	2	0	4	51	10	20	7	2	17	74
Fatigue	22	6	4	5	18	73	16	1	2	1	6	38
Fever	11	6	0	0	0	33	6	9	0	0	0	28
Nausea	10	9	1	0	2	39	11	13	1	0	2	47
Anorexia	16	8	1	0	2	49	15	10	2	0	4	55
Hypertension	11	6	4	0	8	41	17	6	5	0	9	53
Alopecia	6	5	0	0	0	22	7	5	0	0	0	23
Elevated AST	11	5	6	2	16	65	13	7	7	4	21	58
Hepatobiliary/pancreas	4	2	2	1	6	18	3	3	2	0	4	15
Rash/desquamation	3	1	0	0	0	8	3	2	0	0	0	9
Hemorrhage/bleeding	5	9	1	0	2	29	9	7	1	0	2	32
Weight loss	3	5	1	0	2	18	6	2	0	0	0	15
Infection	6	3	2	1	6	24	5	4	1	1	4	21
Constipation	11	7	5	0	10	43	14	5	5	0	9	45
Vomiting	5	7	0	0	0	24	11	2	0	0	0	25
Ascites	12	13	2	0	4	53	13	10	3	0	6	49
Elevated ALT	11	5	5	0	10	41	10	4	4	1	9	36
Hyperbilirubinemia	8	6	2	1	6	33	7	4	2	2	8	28

NOS: not otherwise specified, HFSR: hand-foot skin reaction, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Table 3. Tumor response to combination therapies

Response	*Sunitinib plus TACE* n=51		*Sorafenib plus TACE* n=51	
	n	%	*n*	%
CR/PR	19	37	31	58
SD	15	29	11	21
PD	16	32	11	21
NE	1	2	0	0
Response rate (%)	37 *		58 *	
Disease control rate (%)	66 **		79 **	

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease. p value *0.146 by chi square test, **0.116 by Fisher's exact test

Discussion

In this study, we made some important clinical observations. SU+TACE and SO+TACE were compared in terms of toxicity, treatment response and survival which, to our knowledge, was the first randomized controlled trial to compare the two regimens in the therapy of stage III HCC. Median OS and PFS in the SO+TACE treated group were both significantly higher than that in the SU+TACE treated group. In addition, response rates and disease control were also higher in the SO+TACE treated group (58% and 79%, respectively) compared to SU+TACE group (37% and 66%, respectively), although without statistical significance. Regarding the grade 3 or higher toxicities, higher rates of thrombocytopenia and neutropenia were found in the SU+TACE group. On the other hand, we found frequent occurrence of grade 3 or more severe HFSR in the SO+TACE group.

In the past several years, cancer chemoprevention concerning the use of natural or synthetic agents to inhibit, retard or reverse tumorigenesis, has received more and more attention [20,21]. Demonstrating the underlying mechanisms involved in the anticancer activity will provide valuable evidence for the development of newer anticancer drugs. Sorafenib is a first-line standard chemotherapeutic drug for HCC patients at BCLC stage C [6]. Sunitinib was closely related to frequent toxicities than sorafenib and this might be partially associated with differences in the management of study treatment and the clinical experience. The bleeding effect of sunitinib may be due to its mediated effect on the endothelial cell [22]. Though thrombocytopenia was a common grade 3/4 adverse event in the sunitinib arm, it was not related to bleeding. Although the schedule of 37.5 mg/d sunitinib used in our study was well tolerated in some other tumors [23,24], we found poor tolerance in the advanced HCC patients. Patients treated with SU+TACE showed higher rates of thrombocytopenia and neutropenia in our study. These results were supported by some other previous randomized trials [25].

Potential benefits of the TACE treatment in advanced stage HCC patients were reported in several studies, even after sorafenib was widely accepted as a first-line HCC therapy [26,27]. Despite the negative result obtained from a previous randomized trial [28], Chung et al. [12] have recently indicated that TACE treatment was effective and safe for HCC patients with invasion of the main portal vein and could prolong their survival. In HCC patients with extrahepatic metastases, intrahepatic control using TACE has also been reported to be beneficial with or without sorafenib combination [11]. Similar profiles in terms of objective response and disease control rates following concurrent therapy were obtained in our study and a previous study by Pawlik et al. [29] in which two-thirds of the patients had BCLC stage C disease.

The new results in the present study were that the median OS and PFS in the SO+TACE treated group were both significantly higher compared with the SU+TACE treated group. Besides, response and disease control rates were also higher in the SO+TACE treated group compared to the SU+TACE group, although there was no statistically significant difference. In addition, toxicities of the two regimens were comparable and well-tolerated by most of the patients.

Conclusions

SO+TACE was more effective and well-tolerated in most of the patients with unresectable stage III HCC compared with the SU+TACE regimen. More randomized studies comparing this regimen with SO+TACE are warranted. This regimen may be a better alternative to the current standard regimens. However, the clear mechanisms underlying the sorafenib action and its utility for the treatment of HCC in humans still need to be investigated further.

Conflict of interests

The authors declare no conflict of interests.

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