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ORIGINAL ARTICLE

Sorafenib with TACE improves the survival of hepatocellular carcinoma patients with more than 10 cm tumor: a single-center retrospective study

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Summary

Purpose: *Sorafenib, a multikinase inhibitor, is effective in patients with advanced hepatocellular carcinoma (HCC). Transarterial chemoembolization (TACE) is an important palliative treatment for unresectable HCC, but TACE-induced ischemic injury can upregulate angiogenic factors and it might be associated with poor prognosis. The purpose of this study was to evaluate the efficacy of conventional TACE with or without sorafenib in patients with Barcelona Clinic Liver Cancer (BCLC) stage A-B HCC.*

Methods: *Thirty patients with BCLC stage A or B HCC who had undergone TACE were enrolled in this retrospective study. Child–Pugh score, BCLC staging classification, size and number of lesions were recorded. Sorafenib was given 1 month after TACE to some patients who responded to TACE. Repeated TACE was performed on demand. Tumor response was assessed every 12 weeks. The primary objective of this trial was the progression free survival (PFS). Secondary objectives were overall survival (OS), disease control rate (DCR) and total number of TACE interventions. Kaplan-Meier method was used for the estimation of survival and survival curves were compared with Log-rank test.*

Results: *Twenty-five (83.3%) patients had Child-Pugh A and 5 (16.7%) Child-Pugh B, and 24 (80%) patients had BCLC stage B disease and remanining had stage A disease. Lesion size >10 cm was found in 6 patients and 16/7/7 patients had single/two/multiple lesions, respectively. Mean number of TACE was 2.10±1.369. Seventeen (56.7%) patients used sorafenib after TACE whereas 13 (43.3%) patients were followed without any treatment but received consequent TACEs if needed. PFS of all patients was 10 months (range 3-48); it was 13 months for TACE plus sorafenib group and 9 months for TACE group (p=0.081). In subgroup analysis, TACE plus sorafenib group had better PFS (36 vs 12 months) in patients with tumor size > 10 cm (p=0.025). In the analysis of Child-Pugh A cases, PFS of TACE plus sorafenib group was 23 months while it was 10 months in TACE group (p=0.007).*

Conclusion: *Concurrent treatment in Child-Pugh A group HCC with conventional TACE and sorafenib demonstrates a significant efficacy in patients having tumor size >10 cm. In Child-Pugh A group, PFS was superior in the sorafenib plus TACE group than in TACE alone group.*

Key words: *hepatocellular carcinoma, intermediate stage, response rate, sorafenib, transarterial chemoembolization*

Introduction

HCC is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide [1,2]. Surgical resection has been considered as a definitive treatment of HCC, however, most patients are not suitable for resection because the disease is usually detected in advanced stage.The oral multikinase inhibitor sorafenib that targets vascular endothelial growth factor

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receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and Raf signaling is approved in patients with unresectable or advanced HCC based on two phase 3 randomised trials (SHARP and Acian Pacific) [3,4].

Liver transplantation is a potential curative therapeutic option for patients with a single tumor ≤5 cm in diameter or no more than three nodules ≤3 cm in diameter in patients with unresectable HCC and cirrhosis, and the 4-year survival rate is about 85% [5]. Partial hepatectomy is another potentially curative therapy for patients with a solitary tumor with no evidence of gross vascular invasion [6]. Despite the curative treatment approaches, tumor recurrence rate is still high. Five-year recurrence rate for patients treated with resection is about 60-80% and it is about 40-70% for patients treated with percutaneous ethanol injection (PEI), and radiofrequency ablation (RFA) therapies [7-9]. In this regard, the phase III STORM trial was planned to examine the efficacy of sorafenib as adjuvant therapy in patients with HCC showing a complete radiological response after curative treatment by surgical resection or local ablations (PEI or RFA). The results showed that no contribution of sorafenib to time to tumor recurrence was detected, and thus sorafenib is not recommended as adjuvant therapy [10].

TACE is the standard treatment approach for patients with HCC who are not suitable for curative treatments [11] and the 3-year survival rate is about 26% with TACE [12]. Sorafenib possibly acts via blockage of TACE-induced angiogenic factors and potentially enhance TACE's efficacy [13,14]. Addition of sorafenib to TACE in patient with advanced HCC is recomended. However, this issue is controversial for patients with intermediate stage HCC who have responded to TACE.

The aim of the present study was to evaluate whether the combination of TACE and sorafenib could improve the response and survival of patients with TACE-responded HCC and to define the subgroups which are most likely to benefit from added sorafenib according to number and size of lesions and Child-Pugh score.

Methods

The study population consisted of patients with histologically confirmed HCC who were not suitable for resection or liver transplantation defined as three lesions >3 cm or 1 lesion >5 cm according to the BCLC criteria or patients with stage A also eligible for inclusion if they had refused surgery, or if the location of their tumor made them ineligible for surgery and ablation or had comorbidities. Only patients without extrahepatic spread or vascular invasion were eligible. Further inclusion criteria were as follows: age ≥18 years, at least one measurable lesion, Child–Pugh score of ≤9, total bilirubin levels ≤2 mg/dL, albumin level >2.8 g/dL, absolute neutrophil count >1,500/mm^3, platelet count >100,000/ mm^3, hemoglobin >9 g/dL, international normalized ratio (INR) <1.5 the upper limit of normal (ULN) and partial thromboplastin time (PTT) within normal limits, aspartate transaminase (AST) or alanine transaminase (ALT) <5 × ULN, alkaline phosphatase (ALP) <4 × ULN, serum creatinine <1.5 × ULN and Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–2.

Angiography was performed on all patients using the right or left femoral artery. After catheterization of common hepatic artery with diagnostic catheter, microcatheter was placed to the branch of the tumor-feeding hepatic artery. TACE was performed with drug-eluting bead particles that were loaded with 50-100 mg of doxorubicin. After 1 hr of loading doxorubicin into the spheres, it was mixtured with non-ionic contrast medium and injected under fluoroscopic guidance until visible stasis of flow obtained.

TACE was repeated until radiological response was achieved. Standard follow-up evaluation, including contrast-enhanced CT (CE-CT) scans and laboratory assessments, were performed during weeks 4 and 12 and every 12 months after TACE. When radiological response was seen in the first visit with CE-CT, patients were administered sorafenib 400 mg/day BID per os or TACE alone.

The primary objective of this trial was PFS. PFS was defined as the time from the beginning of treatment until disease progression or death according to RECIST 1.0. criteria. The secondary objectives were OS, DCR (complete response [CR] +partial response [PR] +stable disease [SD]), and total number of TACE interventions. OS was measured from the beginning of treatment until the date of death or last visit.

Statistics

Student's t-test was used for the comparison of 2 independent variables with normal distribution. Kaplan-Meier method was used for the estimation of survival probabilities and survival curves were compared with log-rank test. Variables with p values <0.10 according to log rank test in univariate analysis were added to Cox's multivariate regression analysis. SPSS for Windows, version 22.0 pocket program, was used for statistics and $p<0.05$ was considered as statistically significant.

Results

Thirty patients were included in this retrospective study. All patients were Caucasian, 4 (13.3%) females and 26 (86.7%) males, with mean age of 67.7± 9.27 years. Twenty-five (83.3%) pa-

Table 1. Clinical features of two groups

Variables	*TACE*	*TACE+Sorafenib*	*p value*
Age, years			
Median	68	70	0.584
Range	36-79	54-85	
Sex, n (%)			
Male	12 (92.3)	14 (82.4)	0.427
Female	1 (7.7)	3 (17.6)	
Etiology, n (%)			
Hepatitis B	9 (69.2)	9 (52.9)	0.616
Hepatitis C	2 (15.4)	3 (17.6)	
Unknown/Other	2 (15.4)	5 (29.4)	
Child-Pugh class, n (%)			
A	13 (100)	12 (70.6)	0.032
B	0 (0)	5 (29.4)	
BCLC stage, n (%)			
A	3 (23.1)	3 (17.6)	0.713
B	10 (76.9)	14 (82.4)	
Number of HCC nodules, n (%)			
1			0.682
2	6 (46.2)	10 (58.8)	
>2	4 (30.8)	3 (17.6)	
	3 (23.1)	4 (23.5)	
Tumor size (cm), n (%)			
<10	10 (76.9)	14 (82.4)	0.713
≥ 10	3 (23.2)	3 (17.6)	

BCLC: Barcelona Clinic of Liver Cancer

tients were Child-Pugh A and 5 (16.7%) Child-Pugh B. According to BCLC 24 (80%) patients had stage B disease and remaining had stage A disease. Lesion size >10 cm was found in 6 patients and 16/7/7 patients had single/two/multiple lesions, respectively. Mean number of TACE was 2.10±1.369.

Seventeen (56.7%) patients used sorafenib after TACE, whereas 13 (43.3%) patients were followed without any treatment or consequent TACEs if needed. Characteristics of patients for TACE and TACE plus sorafenib group are illustrated in Table 1.

PFS of all patients was 10 months (range 3-48); it was 13 months for the TACE plus sorafenib group and 9 months for the TACE group. There was no statistically significant difference regarding PFS of all patients (p=0.081) (Figure 1). In subgroup analysis, the TACE plus sorafenib group had better PFS (36 vs 12 months, p=0.025) in patients with tumor size >10 cm (Figure 2). In the analysis of Child-Pugh A cases, PFS of the TACE plus sorafenib group was 23 months, while it was 10 months in the TACE-alone group (p=0.007) (Figure 3). There was no statistical difference of PFS regarding BCLC stage.

In multivariate analysis, use of concurrent sorafenib, number of lesions, tumor size and Child-Pugh score were taken into the Cox regression model. Use of concurrent sorafenib resulted in 3.64-fold decreased risk for progression compared to TACE alone group. Child-Pugh A disease decreased the risk for progression by 6.51 times compared to Child-Pugh B patients (Table 2).

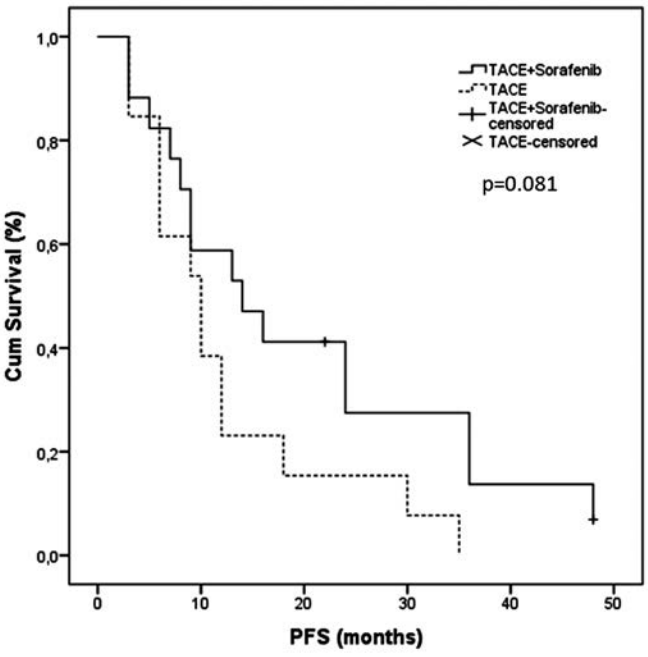

Figure 1. Kaplan-Meier curves for progression-free survival of TACE and TACE plus sorafenib groups.

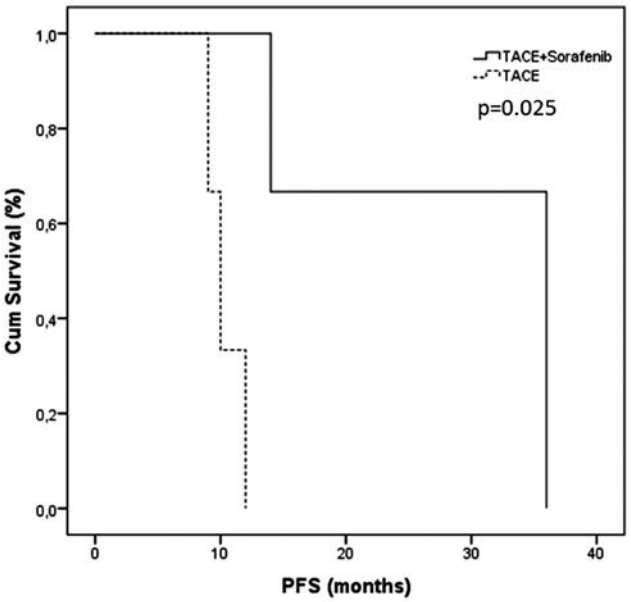

Figure 2. Kaplan-Meier curves for progression-free survival of TACE alone and TACE plus sorafenib group in patients with tumor size more than 10 cm.

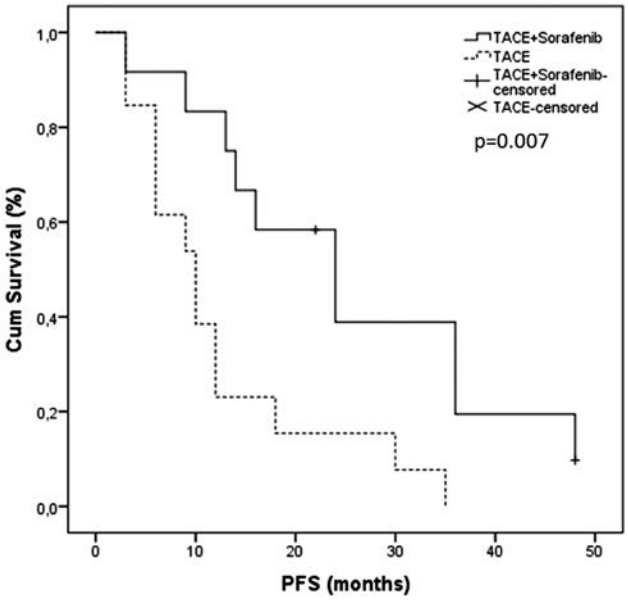

Figure 3. Kaplan-Meier curves for progression-free survival of TACE alone and TACE plus sorafenib group in patients with Child-Pugh A disease.

Table 2. Multivariate Cox regression analysis for progression-free survival

Variables	*P*	*HR*	*95% CI for Exp(B)*	
			Lower	*Upper*
Concurrent sorafenib	0.013	3.640	1.314	10.082
Number of lesions (1)	0.216			
Number of lesions (2)	0.608	0.756	0.260	2.199
Number of lesions (>2)	0.172	2.560	0.664	9.869
Child-Pugh	0.022	6.506	1.305	32.446
Tumor size	0.764	1.171	0.418	3.277

Discussion

Vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), angiopoietins, platelet derived growth factor (PDGF), transforming growth factor (TGF)-beta and mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAPK/ERK) are the key molecules playing important roles in the pathogenesis of HCC [15]. Sorafenib inhibits molecular components of the Raf–MEK–ERK signaling pathway, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-β, thus inhibits neoangiogenesis; this situation might explain the observed survival benefit in advanced HCC [16]. Hypoxia in the center of growing tumors leads to intracellular stabilization of hypoxia-inducible factor (HIF)-1a, and induces expression of several hypoxic response genes, such as VEGF. TACE concentrates on chemotherapeutic agents at the tumor site and blocks the primary artery which is feeding the tumor [17]. However, this procedure can upregulate the local angiogenic factors that facilitate tumor regrowth and this might increase the metastasis risk after TACE [18]. According to two metaanalyses, patients with advanced HCC treated with TACE plus sorafenib had better survival than those treated with TACE [19,20]. Although there have been a lot of studies [21-23] related with intermediate stage HCC with added sorafenib to TACE, it has not been answered whether sorafenib should be added to treatment of TACE-responded patients with HCC. In the present study, we evaluated the clinical outcomes of sorafenib added to TACE-responded patients, 4-6 weeks after TACE, in stage A and B HCC patients and analysed according to number of lesions, sizes and Child-Pugh scores. We found that stage B patients, especially with lesion size >10 cm, showed better PFS.

A number of phase II or III studies were conducted to assess the contribution of sorafenib in patients with intermediate stage. There have been different ways to combine TACE and sorafenib: after or before TACE; concurrent TACE or as an interruption for TACE sessions. Phase II SOCRATES trial assessed patients with intermediate

and advanced stage HCC. Thirty-three patients with stage B HCC were included and sorafenib was given 14 days before TACE. For patients with Child–Pugh A, BCLC-B, and who had received at least one TACE session, TTP was 16.4 months and PFS 12.9 months (95 % CI 6.5–∞) [24]. In another prospective phase II study, sorafenib was administered 3 days after TACE in 41 patients with intermediate stage HCC, and TTP was 7.3 months [25]. An Italian randomized study with 62 patients showed an improved TTP of 9.2 months for the sequential TACE plus sorafenib therapy (sorafenib was started after one months from TACE and was interrupted during the TACE sessions) compared to 4.9 months for the TACE monotherapy in patients with intermediate HCC stage related with hepatitis C (p<0.01) [26]. The phase II START trial investigated the safety and efficacy of sorafenib combined with conventional TACE in patients with BCLC stage A (n=32) and B (n=154) (sorafenib was started concurrently and interrupted 4 days before and after TACE). In this study the median TTP was reported as 5.4 months for the TACE plus sorafenib group and 3.7 months in the placebo group; these results were lower compared with previous studies. In contrast, a phase III study which was conducted by Kudo et al. did not show survival benefit with sorafenib in patients with unresectable HCC treated with sorafenib after TACE. Negative results may have been obtained in this study since sorafenib started 9 weeks after TACE in patients who responded to TACE [27].

The phase II SPACE trial which included the highest number of patients with stage B HCC, compared concomitant sorafenib with placebo in patients who had undergone drug-eluting bead (DEB)-TACE. Median TTP for the sorafenib plus DEB-TACE group was 169 days (95%CI, 166-219), while it was 166 days (95%CI, 113-168) for the placebo plus DEB-TACE group (p=0.072) [28]. Subgroup analysis according to number of lesions, tumor size and Child-Pugh score were not recorded in this study. These statistical values were similar with the results of our study (p=0.081). However, we showed a statistically significant survival benefit of sorafenib in patients with tumor size >10 cm (p=0.025) and Child-Pugh A cases (p=0.007). In this regard, subgroup analysis should be done to identify the patients who can have the maximum benefit from the addition of sorafenib in previous studies.

In multivariate analysis, tumor size ≥5 cm, 5 or more tumors, and extrahepatic disease were identified as predictors of poor prognosis following TACE [29]. Other authors reported that complete necrosis rate of tumor tissue after TACE was about 10-20%, while for large HCCs it was much lower and the large tumor lesions were associated with a low survival for patients with HCC [30,31]. Also, it was shown that the risk of vascular invasion increases with tumor size, especially ≥10 cm, for patients who were planned to undergo resection [32]. A study conducted in patients with advanced HCC who were administered TACE and sorafenib showed that tumors >10 cm had a lower survival compared to <10 cm tumors (HR 1.804; 95%CI 1.270–2.562; p= 0.001) [33]. However, literature lacks information about subgroup analysis according to the number and size of tumors for patients with intermediate stage HCC. In our analysis, it was shown that patients with tumor size >10 cm had the main PFS benefit compared with patients with tumor size <10 cm.

The main limitations of our study were its retrospective design, relatively low number of patients and lack of toxicity evaluation. Yet, this study can pave the way of designing new prospective studies investigating the answer of "Which subgroup should use sorafenib in TACE-responded HCC patients?".

Conclusion

Concurrent treatment of stage B HCC with conventional TACE and sorafenib demonstrates a significant efficacy in patients having >10 cm tumor size and only Child-Pugh A score.

Conflict of interests

The authors declare no confict of interests.

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