

Original Paper

Combined Transarterial Embolization/ Chemoembolization-Based Locoregional Treatment with Sorafenib Prolongs the Survival in Patients with Advanced Hepatocellular Carcinoma and Preserved Liver Function: A Propensity Score Matching Study

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Keywords

Sorafenib · Transarterial chemoembolization · Advanced HCC · Child-Pugh A

Abstract

Background: Sorafenib is the standard treatment for patients with Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma (HCC). However, the treatment outcome is not satisfactory. We retrospectively analyzed whether adding transarterial embolization/chemoembolization (TA(C)E)-based locoregional therapy to sorafenib can further improve treatment efficacy. **Patients and Methods:** We included 147 BCLC stage C HCC patients with Child-Turcotte-Pugh class A liver function and treated with sorafenib for analysis. Through propensity score matching, we divided patients into the combined treatment group ($n = 63$; patients received TA(C)E-based locoregional treatment and sorafenib) and the sorafenib monotherapy

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group ($n = 63$). We analyzed the effects of patients' clinical and tumor-related factors on their overall survival (OS) and time to tumor progression. **Results:** The OS was better in the combined treatment group than in the sorafenib monotherapy group (419 vs. 223 days, $p = 0.028$). In the Cox regression model, combined treatment, a lower baseline α -fetoprotein (AFP) level <400 ng/mL, tumors without main portal venous tumorous thrombosis, and age ≥ 60 years were identified as independent factors for OS. Subgroup analysis demonstrated that patients with a higher baseline AFP level >400 ng/mL, age <60 years, tumors with branched portal venous tumorous thrombosis only or without extrahepatic metastasis benefited the most from combined treatment. **Conclusion:** Combining TA(C)E-based locoregional treatment with sorafenib resulted in better OS in patients with BCLC stage C HCC compared with sorafenib alone. TA(C)E-based locoregional treatment can be an adjunctive treatment to sorafenib for patients with advanced HCC and a satisfactory liver functional reserve.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the second leading cause of cancer deaths [1]. According to the Barcelona Clinic Liver Cancer (BCLC) staging system, approximately 40% of patients with HCC are first diagnosed in an advanced stage (i.e., BCLC stage C) with macrovascular invasion and/or extrahepatic metastasis (EHM) [2, 3]. The treatment of patients with advanced HCC is difficult because portal hypertension or portosystemic shunt may develop if a tumor invades intrahepatic vessels; curative treatment is often impossible because of EHM or macrovascular invasion. Furthermore, most patients have concomitant poor liver function due to cirrhosis, making the treatment more challenging. The prognosis of advanced HCC is, therefore, considerably poor with an estimated median overall survival (OS) duration of 6 months [4, 5], and only 25% of patients survive for 1 year [6].

Sorafenib, an oral multikinase inhibitor with antiangiogenic activity, is the first line of treatment for patients with advanced HCC, and has a proven benefit on the OS of patients [7, 8]. However, its efficacy is limited with median OS prolonged for only 2–3 months, and most patients have a limited tumor response [7, 8].

Transarterial chemoembolization (TACE) is recommended for unresectable, intermediate-stage HCC according to clinical guidelines [3, 9]. TACE can cause tumor death through hypoxia and cytotoxic drugs. Sorafenib can inhibit TACE-induced tumor angiogenesis. Therefore, a combination of both may help to control tumors synergistically and has been employed in several studies with variable success [10–12].

TACE, alone or combined with sorafenib, has proven to be safe and tolerable for patients with HCC and portal vein invasion [13–18]. However, the efficacy of such combination is still inconclusive due to the following reasons: (1) studies limited by retrospective cohort design with potential selection bias, (2) mixed study groups with intermediate and advanced HCC, (3) variable liver function of patients including Child-Turcotte-Pugh (CTP) class A and B, (4) comparing sorafenib and TACE combination with TACE alone instead of direct comparison with sorafenib [19, 20].

Currently, only the study conducted by Choi et al. [21] employed a propensity score matching (PSM) cohort and compared the efficacy of the TACE and sorafenib combination with sorafenib alone. In this study, patients with advanced HCC and CTP class A or B liver function were both included. Their results demonstrated a beneficial effect of combined treatment on time to tumor progression (TTP) but not on OS.

The GIDEON study is a real-world, postmarketing study [22]. The data revealed a notably significant improvement in OS across BCLC stages in patients treated with concomitant sorafenib and TACE compared with patients treated with sorafenib alone. However, this study has significant heterogeneity in liver functions and tumor invasiveness patterns between groups.

Zhang et al. [23] included BCLC stage C HCC patients with main portal venous thrombosis and CTP class A/B liver function. They reported that TACE combined with sorafenib offered no additional benefit in terms of OS and TTP to sorafenib, and potential side effects were observed related to TACE in the combined treatment arm. Bolondi et al. [24] reported that a significantly different OS among BCLC B stage HCC patients was noted after stratifying treatment according to patients' liver function and tumor burden [25]. The results of Zhang et al. [23] may, therefore, point out aggressive treatment can be deleterious in patients with limited liver function reserve and high tumor burden.

In the current study, we enrolled patients who had BCLC stage C HCC and CTP class A liver function. By using the propensity score matching method, we investigated whether combining transarterial (chemo)embolization (TA(C)E)-based locoregional treatment with sorafenib can improve the survival outcome of these patients.

Patients and Methods

Patients

From August 2012 to May 2015, we retrospectively enrolled patients who were diagnosed with BCLC stage C HCC due to macrovascular invasion and/or EHM, and treated with sorafenib for charts and images review. All patients were followed for survival and disease progression until the end of October 2016.

In this study, 240 sorafenib-treated patients with BCLC stage C HCC with a satisfactory liver reserve (CTP class A) were included. Patients were excluded if their baseline α -fetoprotein (AFP) data were missing ($n = 6$) or their etiology of liver disease was unknown ($n = 24$). To analyze whether TA(C)E-based locoregional treatment can improve the survival outcomes of patients treated with sorafenib, we excluded patients who underwent locoregional treatment that did not include TA(C)E ($n = 63$). Since the effects of transarterial embolization (TAE) and TACE on tumor were considered equivalent [26, 27], we also enrolled patients who underwent TAE without any chemotherapy agent (i.e., bland TAE). Of the 240 patients, 147 were finally enrolled. They were divided into the sorafenib monotherapy group (sorafenib monotherapy group, $n = 68$) and the sorafenib combined with TA(C)E-based locoregional treatment group (combined treatment group, $n = 79$). The patients we included were fitted to the estimated sample size (minimum of 120 patients required to make inferences) if we set the hazard ratio (HR) at 0.6 based on the previous studies [7, 8], using a two-sided α -value of 0.05 and power of 80% ($\beta = 0.20$).

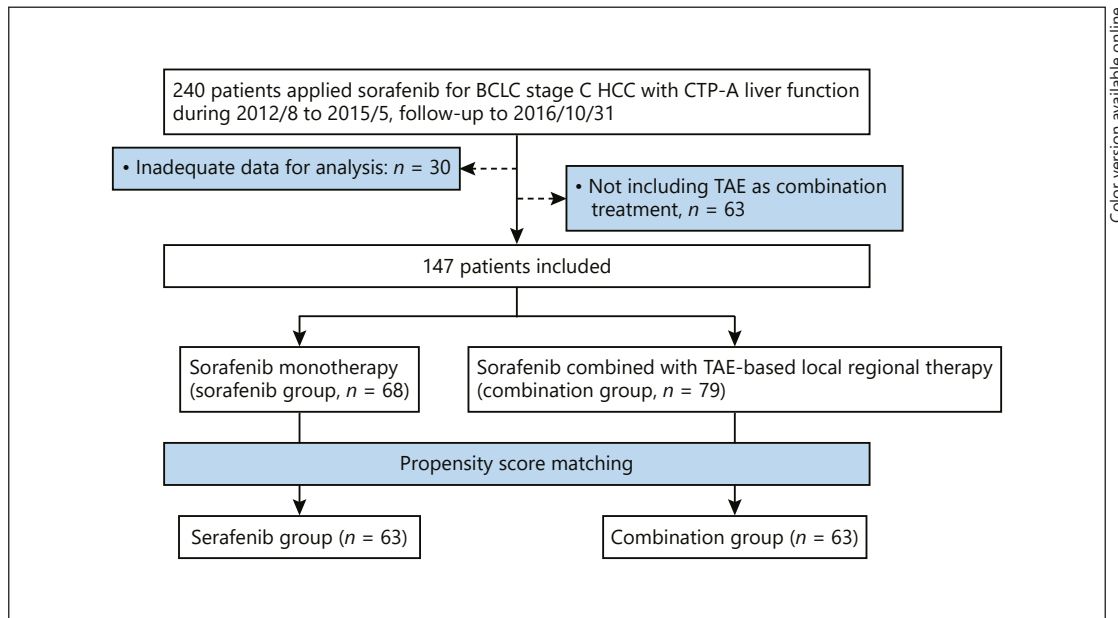
In the combined treatment group, patients were treated with sorafenib and TA(C)E, with or without other locoregional treatments, including external beam radiation therapy, hepatic arterial infusion chemotherapy, selective internal radiation therapy, radiofrequency ablation, and percutaneous ethanol injection. The detailed data of selection algorithm are shown in Figure 1.

HCC Diagnosis and Sorafenib Therapy

HCC was diagnosed using the radiological or histological method according to the European Association for the Study of the Liver guidelines [9].

The cost of sorafenib was reimbursed by Taiwan's National Health Insurance (NHI) administration or at a patient's own expense. Prior to sorafenib administration, blood examinations were performed, and liver function was determined. Through these examinations, eligibility for sorafenib therapy was reviewed by Taiwan's NHI administration. The cost of sorafenib was covered by the NHI only if a patient presented with BCLC stage C HCC with macroscopic vascular invasion and/or EHM and a satisfactory liver function (i.e., CTP class A).

For patients with no risk factors, the initial dose of sorafenib was 400 mg twice a day. During sorafenib treatment, the daily dose could be reduced by each attending physician according to the grades of adverse events (AE) or the Eastern Cooperative Oncology Group (ECOG) performance status. After the initiation of



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Fig. 1. Study algorithm.

sorafenib therapy, the response of patients to the treatment was evaluated every 8–12 weeks by using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) [28]. Sorafenib treatment was continued until disease progression, unacceptable drug-related toxicity, decompensated liver failure, or the patient’s wish to discontinue treatment.

Decision for TA(C)E Treatment and Other Locoregional Therapy

The suggestion of adding TA(C)E or other locoregional therapy to sorafenib was made according to the discussion results of HCC multidisciplinary team which was composed of hepatologists, oncologists, surgeons, radiologists, and radio-oncologists. The major consideration of treatment included baseline liver function, tumor burden, and ECOG performance status. All the suggested treatments were done after achieving a consensus with patients and their caregivers.

The TA(C)E sessions were conducted on demand, without interruption of sorafenib. The decision to undergo next TA(C)E was mainly based on a previous result of treatment which showed stable disease at least and without presence of contraindication (e.g., liver decompensation) for TA(C)E. The chemotherapy agent administered for TACE was doxorubicin. Embolization agents administered were gelfoam plus lipiodol (mixed or not mixed with doxorubicin), small particle beads (Embozene), or drug-eluting beads (DC Bead, Tandem, Hepasphere).

Data Collection and Study Design

Each patient’s baseline clinical data including age, sex, date of diagnosis, etiology of liver disease, CTP score, tumor characteristics (number of tumors, maximal tumor size, presence and extent of portal vein invasion and site of metastases), and AFP levels were collected from patients’ medical record and imaging. The session and modality of treatment that patients received and the tumor response to treatment were also reviewed.

According to the imaging studies, we classified the extent of portal vascular tumoral thrombosis (PVTT) as none, branched (not in the main trunk of the portal vein), or main (invasion in the main trunk of the portal vein or beyond) and determined the extent of EHM using the mRECIST criteria [28]. High or low tumor burden was classified whether the tumor volume was more or less than half of the liver volume.

Our study was approved by the Institutional Review Board of National Cheng Kung University Hospital. Due to its retrospective nature, and as only chart review was done, the requirement of written informed consent was waived for this study.

Table 1. Baseline characteristics of entire cohort before match (*n* = 147)

Characteristics	Median (range) or <i>n</i> (%)
Age, years	61 (33–87)
Gender	
Male	104 (70.7%)
female	43 (29.3)
ECOG	
0	140 (95.2%)
1	7 (4.8%)
Etiology of liver disease	
HBV	98 (66.7%)
HCV	43 (29.3%)
HBV+HCV	6 (4.1%)
CTP score	
5	108 (73.5%)
6	39 (26.5%)
Albumin	
>3.5 g/dL	129 (87.8%)
≤3.5 g/dL	18 (12.2%)
Bilirubin	
<2 mg/dL	146 (99.3%)
≥2 mg/dL	1 (0.7%)
PT prolong	
<4 s	145 (98.6%)
≥4 s	2 (1.4%)
Ascites	
Absent	129 (87.8%)
Present	18 (12.2%)
AFP	
<400 ng/mL	78 (53.1%)
≥400 ng/mL	69 (46.9%)
Tumor burden	
<50%	121 (82.3%)
≥50%	26 (17.7%)
Morphology	
Nodular	128 (87.1%)
Infiltrative	19 (12.9%)
EHM	62 (42.2%)
Indication of sorafenib	
Branch	26 (17.7%)
Main PVTT	41 (27.9%)
EHM+PVTT	18 (12.2%)
TACE-based local regional therapy during sorafenib	
Yes	79 (53.7%)
No	68 (46.3%)
Pure sorafenib	68 (46.3%)
Type of local regional therapy	
TACE+sorafenib	43 (29.3%)
TACE+other+sorafenib	36 (24.5%)

EHM, extrahepatic metastasis; PVTT, portal venous tumor thrombosis.

Table 2. Demographic table before and after match

	Before match (n = 147)					After match (n = 126)				
	monotherapy		combined treatment		p value	monotherapy		combined treatment		p value
	n = 68	%	n = 79	%		n = 63	%	n = 63	%	
Age										
<60 years	30	44.1	37	46.8	0.74	29	46.0	30	47.6	1
≥60 years	38	55.9	42	53.2		34	54	33	52.4	
Gender										
Male	42	61.8	62	78.5	0.03	42	66.7	15	23.8	0.32
Female	26	38.2	17	21.5		21	33.3	48	76.2	
ECOG										
0	66	97.1	74	93.7	0.45	61	96.8	61	96.8	1.00 ^a
1	2	2.9	5	6.3		2	3.2	2	3.2	
Etiology										
HBV	43	63.2	55	69.6	0.47	43	68.3	44	69.8	0.90 ^a
HCV	23	33.8	20	25.3		18	28.6	16	25.4	
HBV+HCV	2	3.0	4	5.1		2	3.2	3	4.8	
CTP score										
5	46	67.6	62	78.5	0.14	44	69.8	50	79.4	0.22
6	22	32.4	17	21.5		19	30.2	13	20.6	
Albumin										
>3.5 g/dL	60	88.2	69	87.3	0.87	55	87.3	57	90.5	0.78
≤3.5 g/dL	8	11.8	10	12.7		8	12.7	6	9.5	
Bil-T										
<2 mg/dL	67	98.5	79	100	0.46	62	98.4	63	100	1 ^a
≥2 mg/dL	1	1.5		0		1	1.6	0	0	
PT										
<4 s	66	97.1	79	100	0.21	61	96.8	63	100	0.50 ^a
>4 s	2	2.9	0			2	3.2	0	0	
Ascites										
Absent	57	83.8	72	91.1	0.18	55	87.3	56	88.9	1
Present	11	16.2	7	8.9		8	12.7	7	11.1	
AFP										
<400 ng/ml	37	54.4	41	51.9	0.76	32	50.8	31	49.2	1
≥400 ng/ml	31	45.6	38	48.1		31	49.2	32	50.8	
ALBI grade										
1	39	57.4	54	68.4	0.17	35	55.6	43	68.3	0.14
2	29	42.6	25	31.6		28	44.4	20	31.7	
Tumor burden										
<50%	56	82.4	65	82.3	0.99	52	82.5	51	80.9	1
>50%	12	17.6	14	17.7		11	17.5	12	19.1	
Morphology										
Nodular	63	92.6	65	82.3	0.06	58	92.1	53	84.1	0.27
Infiltrative	5	7.4	14	17.7		5	7.9	10	15.9	
PV invasion										
Branch or absent	37	54.4	59	74.7	0.01	37	58.7	44	69.8	0.26
Main	31	45.6	20	25.3		26	41.3	19	30.2	
EHM										
Yes	35	51.5	41	51.9	0.96	35	55.6	31	49.2	0.48
No	33	48.5	38	48.1		28	44.4	32	50.8	
Sorafenib-specific AE ^a										
Yes	40	60.6	53	75.7	0.06	38	61.3	40	74.1	0.14
No	26	39.4	17	24.3		24	38.7	14	25.9	
Type of therapy										
Pure sorafenib	68	100.0	–	–	–	63	100	–	–	–
TACE + sorafenib	–	–	43	54.4	–	–	–	34	54.0	–
TACE + other treatment + sorafenib	–	–	36	45.6	–	–	–	29	46.0	–
TACE type										
cTACE/TAE	–	–	103	65.2	–	–	–	74	60.7	–
Small particle TACE	–	–	25	15.8	–	–	–	21	17.2	–
Deb-TACE	–	–	31	19.6	–	–	–	27	22.1	–

ALBI, albumin-bilirubin; Deb-TACE, drug-eluting bead TACE. ^a Skin rashes/hand-food skin reaction/hypertension/diarrhea.

Statistical Analysis

We compared the baseline characteristics of the combined treatment and sorafenib monotherapy groups by using the χ^2 test or Fisher's exact test for categorical data, as appropriate. Two-tailed sample *t* test was used to analyze continuous variables. For analyzing serial change of laboratory data in each individual patient, a paired *t* test was applied.

To avoid selection bias in this nonrandomized retrospective cohort study, we used the PSM method to match the two treatment groups. Factors that can bias the choice of treatment were identified by using a logistic regression model, which included the ECOG performance status, age, sex, etiology of disease, baseline liver function, tumor burden and morphology, extent of PVTT, and baseline AFP level. After calculating the propensity score, we matched the two groups alongside each other by using the nearest-neighbor matching method without replacement. The PSM was performed using the SAS Macro [29].

We calculated OS from the first day of sorafenib treatment until November 2016 or death from any cause. The survival times and rates of the combined treatment and sorafenib monotherapy cohorts were calculated. The differences in survival rates between the two cohorts were analyzed using a log-rank test. We employed a Cox proportional hazards regression model for univariate and multivariate analyses (by forward stepwise) of prognostic factors. A p value of <0.05 was considered significant. We further performed subgroup OS analysis for patients that underwent combined or monotherapy treatment to identify patients that may benefit more from combined treatment.

The propensity score and matching methods were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA.) The survival analysis, Cox regression, χ^2 test, Fisher's exact test, and t test were performed using SPSS, version 22 (IBM, Armonk, NY, USA).

Results

Baseline Clinical Characteristics

A total of 147 patients were included for the propensity score analysis. After matching, 126 comparable patients (63 matched pairs) were selected for OS and TTP analysis. The demographic data of the patients before propensity score matching are listed in Table 1. The median age of the entire cohort was 61 years (range: 33–87 years) with male predominance. Most of the patients had HBV mono-infection, good liver function reserve – CTP A5, good performance status of ECOG 0, and low tumor burden. More than one-third of the patients had main PVTT, and 42% patients had EHM. The combined treatment cohort had more men and more patients with an infiltrative tumor. The sorafenib monotherapy cohort had more patients with main PVTT. After propensity matching, all factors became equally distributed in the two groups (Table 2).

Treatment Modalities and Outcomes in the Propensity Score-Matched Cohort

In the combined treatment cohort, all of the patients underwent at least one TA(C)E (range: 1–8 sessions). In total, 122 sessions of TA(C)E were done, and of them 56 sessions were conventional TACE (45.9%), 18 sessions were bland TAE (14.8%), 27 sessions were drug-eluting beads TACE (22.1%), and 21 sessions were microsphere TACE (17.2%). In addition to TA(C)E, 46.0% (29/63) of patients in the combined treatment cohort also received other locoregional therapy.

The median survival of the entire cohort was 343 days (range: 15–1,544 days). The cumulative 6-month, 1-year, 2-year, and 3-year survival rates were 63, 48, 20, and 13%, respectively. The combined treatment cohort had better OS than sorafenib monotherapy cohort (median OS: 419 vs. 233 days, $p = 0.028$, Fig. 2a). However, whether patients received combined treatment or sorafenib monotherapy had no significant difference on TTP (median TTP: 146 vs. 84 days, $p = 0.094$, Fig 2b).

As shown in Figure 3, additional locoregional treatment in patients who received TA(C)E had no effect on OS or TTP compared with patients who only underwent TA(C)E (OS: 397 vs. 425 days, $p = 0.48$; TTP: 146 vs. 140 days, $p = 0.71$).

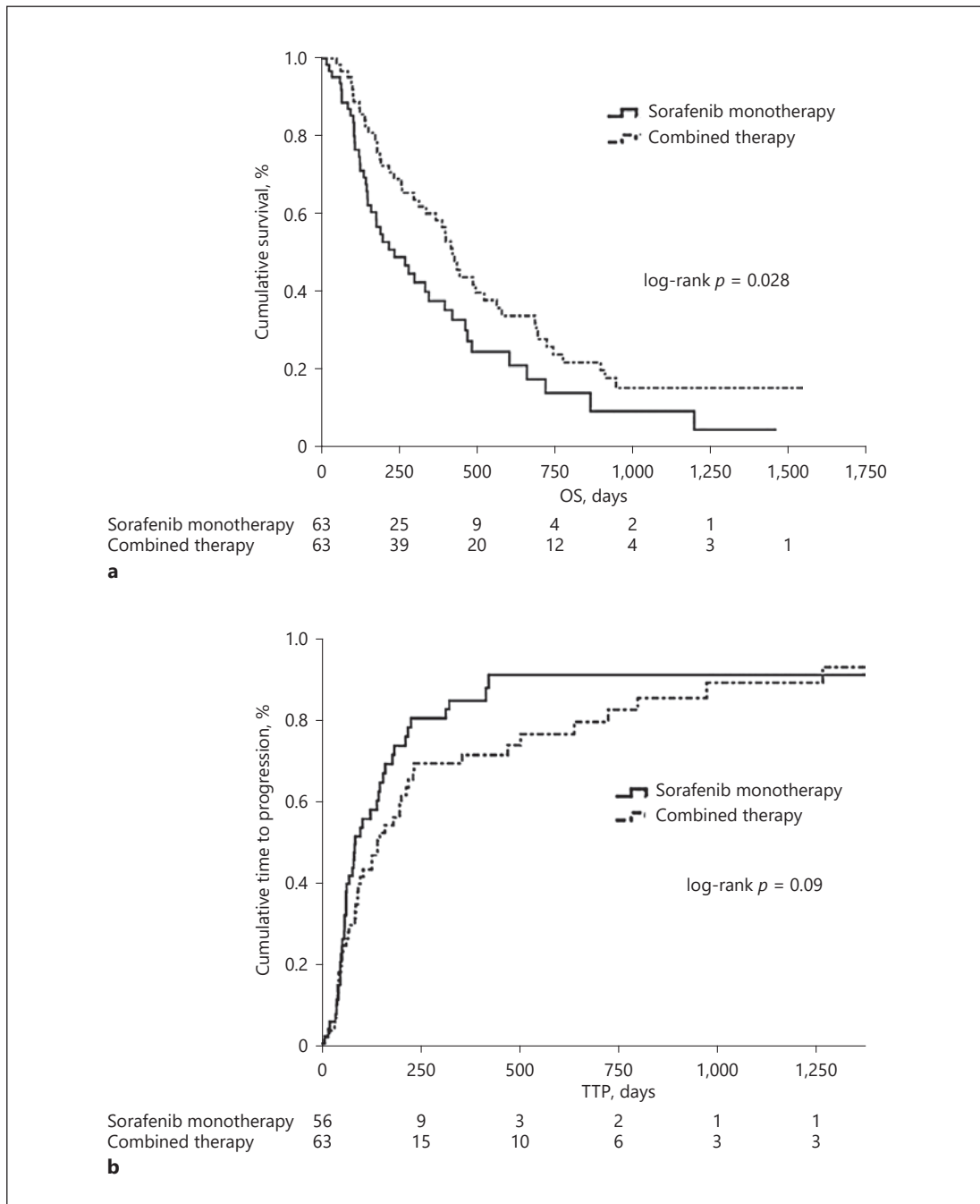


Fig. 2. Kaplan-Meier curves for overall survival (OS) **(a)** and time to tumor progression (TTP) **(b)** of combined treatment and monotherapy groups. **a** Significant difference in OS between the combined treatment and sorafenib monotherapy groups (median OS: 419 vs. 233 days, log-rank $p = 0.028$). **b** No significant difference in TTP between the combined treatment and sorafenib monotherapy groups (median TTP: 146 vs. 84 days, log-rank $p = 0.09$).

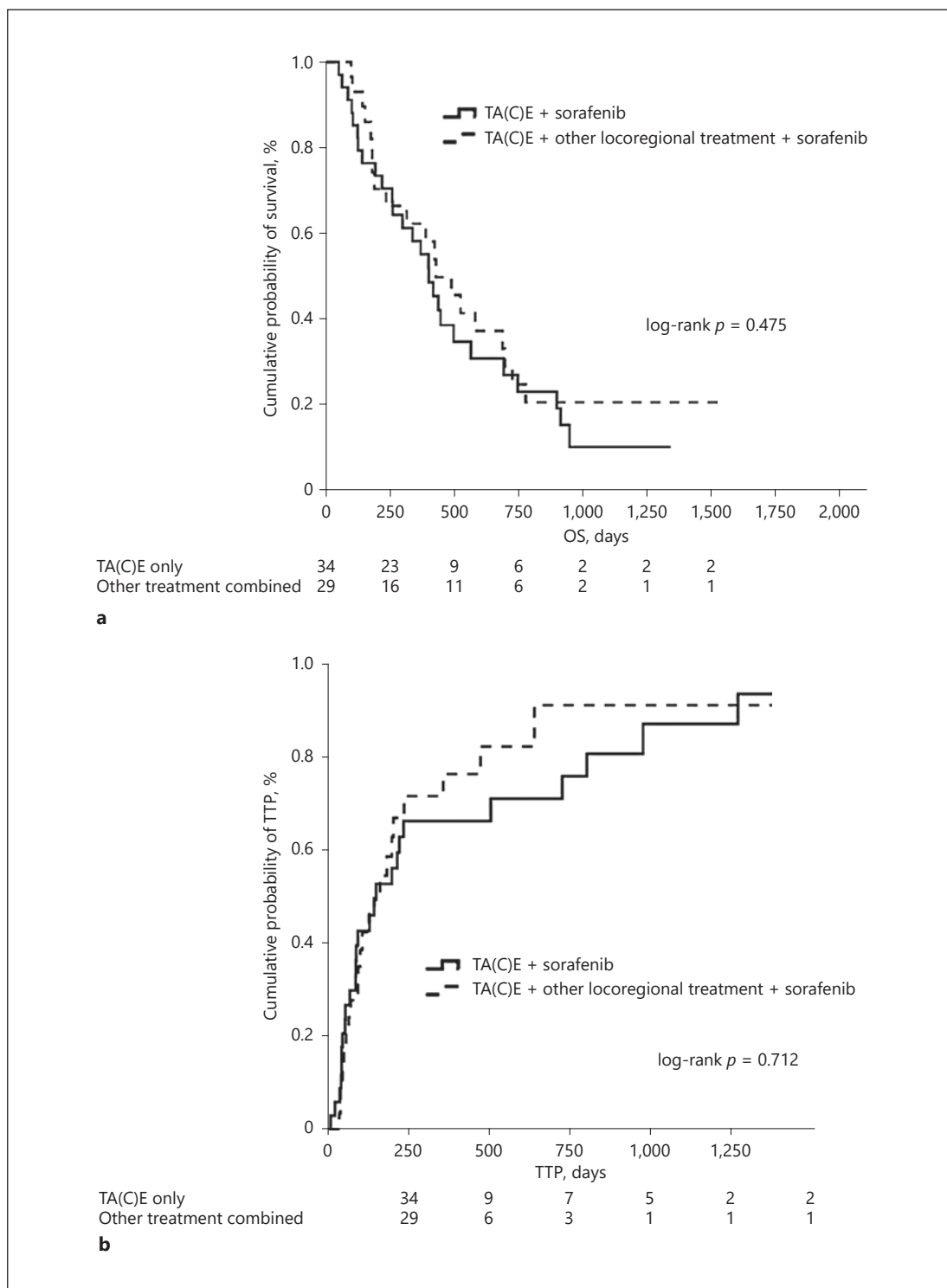


Fig. 3. Kaplan-Meier curves for overall survival (OS) **(a)** and time to tumor progression (TTP) **(b)** of patients who received TA(C)E and sorafenib with or without other locoregional treatment. No significant difference in OS or TTP between these two groups (OS: 425 days for those with other locoregional treatments vs. 397 days for those without, $p = 0.48$, and TTP: 140 days for those with other locoregional treatments vs. 146 days for those without, $p = 0.71$).

Table 3. Univariate and multivariate analysis for OS and TTP

	Overall survival			Time to progression		
	univariate analysis		multivariate analysis	univariate analysis		multivariate analysis
	crude HR (95% CI)	p value	adjusted HR (95% CI)	crude HR (95% CI)	p value	adjusted HR (95% CI)
Treatment						
Combined vs. sorafenib alone	0.63 (0.41–0.95)*	0.03	0.57 (0.33–0.81)*	0.70 (0.47–1.07)	0.10	0.70 (0.46–1.07)
Degree of PV invasion						
Not main vs. main	0.56 (0.36–0.86)*	0.01	0.57 (0.36–0.89)*	0.89 (0.57–1.38)	0.60	–
EHM						
Negative vs. positive	1.05 (0.69–1.60)	0.82	–	1.17 (0.77–1.77)	0.46	–
Age						
≥60 vs. <60 years	0.66 (0.44–1.00)*	0.05	0.64 (0.42–0.98)*	0.89 (0.59–1.35)	0.58	–
Gender						
Female vs. male	0.82 (0.52–1.32)	0.42	–	0.79 (0.49–1.25)	0.31	–
ECOG						
0 vs. 1	0.62 (0.22–1.69)	0.35	–	0.72 (0.23–2.28)	0.57	–
Etiology						
HBV	Ref.	0.29	–	Ref.	0.24	–
HCV	0.72 (0.44–1.18)	–	–	0.84 (0.53–1.33)	–	–
HBV+HCV	0.59 (0.21–1.63)	–	–	0.39 (0.12–1.24)	–	–
CTP score						
5 vs. 6	0.62 (0.39–0.98)	0.04	–	0.83 (0.51–1.35)	0.45	–
ALBI grade						
1 vs. 2	0.70 (0.46–1.07)	0.10	–	1.26(0.83–1.92)	0.29	–
Albumin						
≥3.5 vs. <3.5	0.88 (0.44–1.75)	0.71	–	0.78 (0.42–1.47)	0.45	–
Ascites						
No vs. yes	0.68 (0.33–1.02)	0.06	–	0.80 (0.39–1.66)	0.56	–
AFP						
<400 vs. ≥400 ng/mL	0.66 (0.44–0.99)*	0.05	0.54 (0.35–0.83)*	0.70 (0.46–1.06)	0.09	0.67 (0.44–1.02)
Tumor burden						
<50 vs. >50%	0.56 (0.34–0.93)*	0.03	–	0.99 (0.55–1.78)	0.97	–
Morphology						
Nodular vs. infiltrative	0.66 (0.32–1.37)	0.26	–	0.54 (0.26–1.12)	0.10	0.57 (0.27–1.19)
Sorafenib-specific AE						
Yes vs. no	0.66 (0.42–1.04)	0.07	–	–	–	–

* p value <0.05, by forward stepwise Cox regression model.

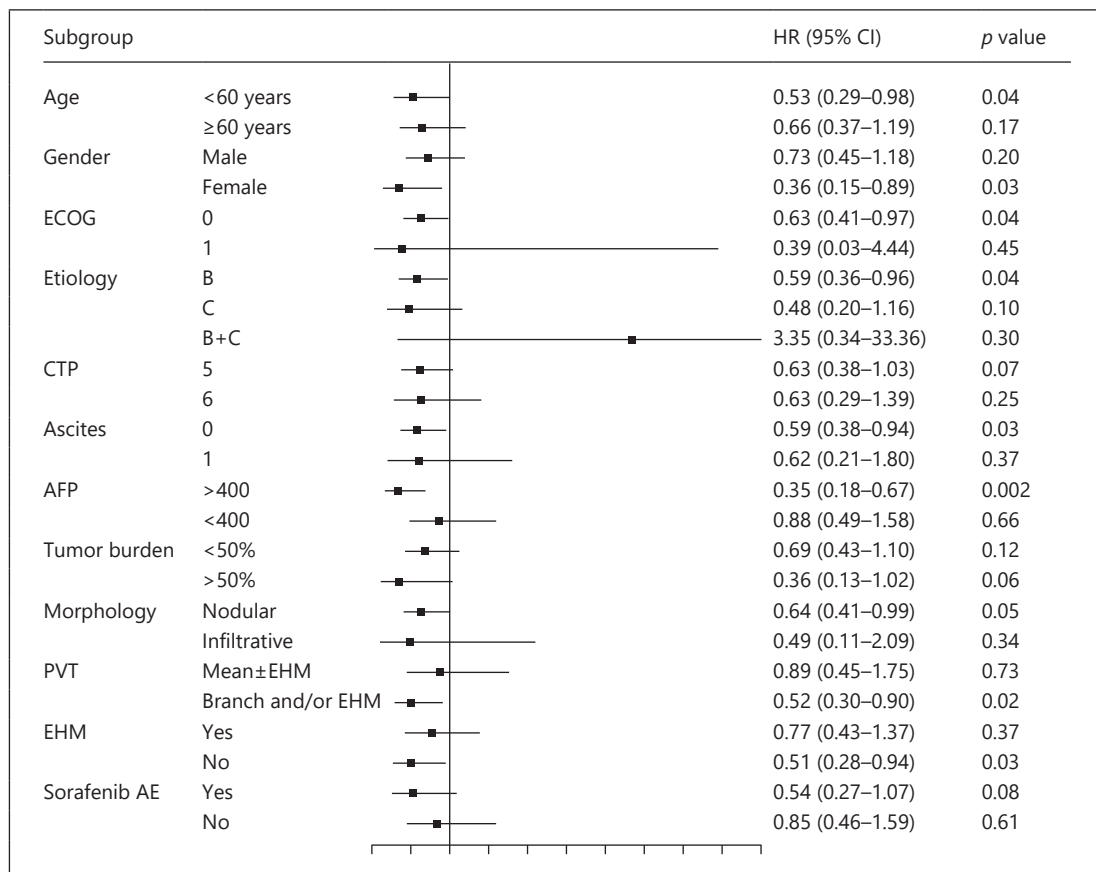


Fig. 4. Subgroup analyses of OS between patients who underwent combined treatment or sorafenib monotherapy. There were survival benefits of combined therapy over sorafenib alone in patients aged <60 years, female, ECOG performance status 0, HBV mono-infected patients, patients without ascites, high baseline α -fetoprotein (AFP) (≥ 400 ng/mL), nodular tumor morphology, tumors without main portal venous invasion, and patients without extrahepatic metastasis (EHM) ($p < 0.05$ for each). CTP, Child-Turcotte-Pugh; PVT, portal vein thrombosis; AE, adverse events.

Predictors of OS and TTP in the Propensity Score-Matched Cohort

The results of univariate and multivariate analyses are shown in Table 3. In the univariate analysis, the combined treatment showed a beneficial effect on OS (HR: 0.63, 95% confidence interval [CI]: 0.41–0.95). Besides, older age ≥ 60 years, tumor without main PVT, good liver function reserve – CTP 5, serum AFP level <400 ng/mL, and low tumor burden also correlated with better survival outcomes.

In the multivariate analysis, the beneficial effect of the combination therapy was still independently significant (adjusted HR: 0.57, 95% CI: 0.33–0.81). Tumor without main PVT, age ≥ 60 years old, and serum AFP level <400 ng/mL also independently predicted a better survival. No prognostic factor associated with TTP was found in either univariate or multivariate analyses.

Subgroup Analysis of the Combined Treatment Cohort

In the subgroup analysis, several factors were found to be associated with significantly better OS in the combined treatment cohort than that of sorafenib monotherapy cohort. These were age <60 years (HR: 0.53, 95% CI: 0.29–0.98, $p = 0.04$), female gender (HR: 0.36, 95% CI:

0.15–0.89, $p = 0.03$), ECOG score of 0 (HR: 0.63, 95% CI: 0.41–0.97, $p = 0.04$), HBV mono-infected patient (HR: 0.59, 95% CI: 0.36–0.96, $p = 0.04$), absence of ascites (HR: 0.59, 95% CI: 0.038–0.94, $p = 0.03$), tumors without main PVTT (HR: 0.52, 95% CI: 0.30–0.90, $p = 0.02$), any PVTT without EHM (HR: 0.51 95% CI: 0.28–0.94, $p = 0.03$), and higher baseline AFP level (HR: 0.35, 95% CI: 0.18–0.67) (Fig. 4).

Treatment-Related AE

Episodes of deterioration of liver function after TA(C)E as indicated by a raised serum bilirubin level of more than 2 mg/dL ($n = 5$, 4.1%), a prolonged prothrombin time 4 s longer than normal control ($n = 3$, 2.5%), or a new onset or worsened ascites/hydrothorax ($n = 12$, 10.7%) were noted in the 122 sessions of TA(C)E. In total, 18 patients had liver function deterioration after TA(C)E, and 11 of them (17.5%) did not have liver function test results that returned to normal. However, there was no statistically significant difference in the mean serum levels of albumin (monotherapy vs. combined therapy, 3.6 vs. 4.29 g/dL, $p = 0.23$) and bilirubin (monotherapy vs. combined therapy, 2.3 vs. 2.67 mg/dL, $p = 0.79$), and duration of prothrombin time (monotherapy vs. combined therapy, 2.2 vs. 1.7 s, $p = 0.35$) between sorafenib monotherapy groups and the combined treatment group 3 months after starting treatment.

Regarding the recorded sorafenib-specific AE (defined as skin rashes, hand-foot skin reaction, hypertension, and diarrhea), 40 of the 54 patients (74.1%) in the combined group and 38 of the 62 patients (61.3%) in the sorafenib monotherapy group had at least one. The difference in the sorafenib-related AE rate was not statistically significant between the two cohorts ($p = 0.14$; Table 4). Besides, the presence of sorafenib-specific AE had no effect on survival (presence vs. absence of AE; median OS: 394 vs. 195 days, $p = 0.07$).

Discussion

Our study demonstrated a survival benefit of combining TA(C)E-based locoregional treatment with sorafenib in the patients with BCLC stage C HCC and satisfactory liver function. In the multivariate analysis, we observed that patients who had tumors without main PVTT, baseline low serum AFP level (<400 ng/mL), who were older (≥ 60 year-old) and had combined treatment had a significantly better OS.

In our study, the median OS of the patients who received sorafenib monotherapy was comparable to that of patients in the SHARP and Asia-Pacific studies [7, 8], but in our study, the median OS was further extended by combining TA(C)E-based locoregional therapy with sorafenib. However, TTP was not significantly different between the patients who did and did not undergo locoregional therapy in addition to sorafenib. This may be explained by the fact that locoregional therapy mainly affects intrahepatic lesions and tumor progression outside the liver remains unchanged. Our subgroup analysis findings that combined treatment added survival benefit to sorafenib monotherapy only in the absence of EHM may further support this hypothesis. The aforementioned SHARP and Asia-Pacific studies have indicated that prolonged OS was not correlated with delay in TTP [30], and we suspected that the survival benefit observed in our patients who underwent the combination treatment was the result of a reduction in tumor burden in the liver, regardless of tumor progression.

Choi et al. [21] reported that both OS and TTP improved in patients with BCLC stage C HCC after receiving combined TACE and sorafenib treatment; however, the improvement diminished and only TTP remained significant after they matched patients with propensity score. Our study supported a combination strategy through demonstrating a survival advantage in our propensity score-matched patients. The major difference between their

Table 4. Adverse events related to treatments

	Combined therapy all events, n (%)	Sorafenib monotherapy, n (%)	p value ^b	Overall, n (%)
<i>TACE-related AE</i>				
Overall TACE sessions	122 (100)			
Fever	58(47.5)			
Abdominal pain	47 (38.5)			
New/worse ascites ^a	9 (7.4)			
New/worse pleural effusion ^a	3 (2.5)			
Bilirubin (elevate more than 2 mg/dL) ^a	5 (4.1)			
Prolonged prothrombin (≥4 s) ^a	3 (2.5)			
AKI (Cr increased ≥0.3 mg/dL)	3 (2.5)			
GI ulcer ^a	9 (7.4)			
Sepsis	7 (5.7)			
Liver abscess	1 (0.8)			
Pulmonary embolism	0 (0)			
SBP	0 (0)			
Acute cholecystitis	1 (0.8)			
Fatigue	3 (2.5)			
Anorexia	2 (1.6)			
Nausea/vomiting/anorexia	5 (4.1)			
<i>Adverse events related to sorafenib</i>				
Skin rash	17 (31.5)	9 (14.5)	0.03	26 (22.4)
HFSR	25 (46.3)	20 (32.3)	0.12	45 (38.8)
Hypertension	7 (13.0)	6 (9.7)	0.58	13 (11.2)
Diarrhea	16 (29.6)	21 (33.9)	0.63	37 (31.9)
Paronychia	1 (1.9)	1 (1.6)	0.92	2 (1.7)
Dry skin	3 (5.6)	1 (1.6)	0.24	4 (3.4)
Pruritus	6 (11.1)	6 (9.7)	0.8	12 (10.3)
Folliculitis	1 (1.9)	2 (3.2)	0.64	3 (2.6)
Mucositis	2 (3.7)	0 (0)	0.08	2 (1.7)
Fatigue/poor appetite	14 (25.9)	11 (17.7)	0.29	25 (21.6)
Nausea/vomiting	4 (7.4)	6 (9.7)	0.66	10 (8.6)
Others	5 (9.3)	6 (9.7)	0.94	11 (9.5)
No record	9 (16.7)	1 (1.6)	0.008	10 (8.6)
Sorafenib-specific AE ^c	40 (74.1%)	38 (61.3%)	0.14	78 (67.2)

^a Compared to before TACE, occurred within 4 weeks from index TACE; ^b By χ^2 or Fisher's exact test; ^c Skin rashes/hand-foot skin reaction/hypertension/diarrhea.

study and ours is that we only included CTP class A patients, whereas their study included a significant portion of patients with CTP class B. As noted, although we selected only CTP A patients for combination treatment, we still had 17.5% of patients who developed irreversible liver functional damage after TA(C)E. Therefore, our study indicated the importance of selecting patients with satisfactory liver reserve for aggressive treatment because the survival benefit of TACE may be attenuated by the associated damage of liver function.

An increased serum AFP level is frequently associated with poorly differentiated HCC, which indicates aggressive tumor behavior and hence a worse survival [31–36]. Our data also showed that a higher baseline AFP level indicated poor OS. Similar to the findings in the study of Choi et al. [21], the survival advantage of combined TA(C)E-based locoregional therapy and sorafenib in our subgroup analysis was more remarkable in patients with HCC with a high

AFP level. This finding may indicate that tumors with an aggressive biological behavior can be additionally controlled by using locoregional treatments, such as TA(C)E.

Our study demonstrated that the patients with tumors having no main PVTT had better survival outcomes. Consistent with our study results, previous studies have reported that not only the presence of a portal vein invasion but also the extent of the portal vein invasion is crucial for determining the survival outcome of patients with BCLC grade C HCC [37, 38]. In the study by Zhang et al. [23], which included patients with HCC and main PVTT, TACE treatment combined with sorafenib resulted in a higher risk of liver decompensation. In their TACE-treated group, the ratio of newly developed ascites, hepatorenal syndrome, and liver dysfunction was high. The deleterious effect of TACE on the liver in patients with main PVTT may explain the lack of additional survival benefit in our patients with main PVTT who underwent the combination treatment.

Age was a contradicting factor for the survival outcome in our study. The patients aged ≥ 60 years had a better survival outcome than the younger patients in our cohort, whereas in subgroup analysis, age < 60 years had a survival advantage in the patients who underwent the combination treatment. The finding that the older patients who were administered sorafenib had a better survival outcome was not identified in previous reports, and this may be related to the older patients in our study having lower tumor burden (data not shown), or other unmatched potential confounders. Although tumor burden was not a significant factor for the survival outcome in our study, it has been related to patient survival in other studies [35, 36, 39]. The superior survival outcome in our older patients may thus be a result of potential confounders. Previous studies have reported that young age is a favorable factor for the survival outcome because young patients usually have a better organ reserve and better performance, allowing them to undergo further aggressive treatments, such as the locoregional treatments performed in our study, and therefore obtain a better outcome.

In addition to sorafenib, various treatment modalities have been applied to patients with BCLC stage C HCC. Of them, TACE is the most common suggested treatment to be combined with sorafenib and no other single treatment has proven to be effective when combined with sorafenib in prolonging the survival of patients with advanced HCC. Our study also failed to demonstrate a survival benefit after adding other treatment modalities such as radiofrequency ablation or external beam radiation therapy to TA(C)E and sorafenib combination treatment. It therefore remains inconclusive whether combining multiple locoregional treatments with TA(C)E and sorafenib can further improve the survival of patients with advanced HCC.

Several studies have mentioned that AE during sorafenib treatment were associated with a favorable survival outcome [40–46]. In these studies, dermatologic AE, diarrhea, and hypertension, which we analyzed, were the most frequently reported events. However, we were not able to find any survival benefit that would be linked to the presence of any of them. This may be due to the relative small sample size and presence of missing data ($n = 10$) in our study.

Due to the retrospective nature of this study, the interpretation of our results is limited by the selection criteria of patients for different treatments. However, we used the PSM method to reduce potential selection bias as much as possible. For the same reason, we were also unable to match the mean daily dosing of sorafenib between the two patient groups. However, the dosing may not have had a considerable impact on survival because no previous studies, including the GIDEON study, have been able to demonstrate a dose-response effect of sorafenib.

In conclusion, we demonstrated that for patients with BCLC stage C HCC and CTP A liver reserve function, combined TA(C)E-based locoregional therapy with sorafenib resulted in better OS compared with sorafenib monotherapy. Based on our preliminary results, we

suggest combined TA(C)E-based locoregional therapy with sorafenib for patients who are less than 60 years old, have good liver functional reserve and performance status, with tumor involvement confined to the portal vein branch, or high serum AFP.

Disclosure Statement

None of the authors has conflicts of interest to disclose concerning this study.

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