Transarterial infusion chemotherapy with FOLFOX for advanced hepatocellular carcinoma: a multi-center propensity score matched analysis of real-world practice

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Background: To compare the treatment effectiveness and safety among transarterial infusion chemotherapy (TAI) with FOLFOX regimen, transarterial chemoembolization (TACE), and sorafenib in patients with BCLC stage C hepatocellular carcinoma (HCC).

Methods: The data of consecutive patients with BCLC stage C HCC treated with TAI, TACE, or sorafenib from January 2015 to December 2018 at three centers were retrospectively analyzed. Propensity-score matched (PSM) analysis was pairwise performed to reduce selection bias. Treatment effectiveness and safety were evaluated and compared using the Kaplan-Meier method, log-rank test, Cox regression models, and χ^2 test.

Results: The median overall survival (OS) in the matched TAI cohort was significantly longer than the sorafenib cohort (19.6 *vs.* 7.5 months, $P=0.009$), and the TACE cohort (estimated 27.8 *vs.* 6.6 months, $P<0.001$). The difference in median progression-free survival (PFS) between the matched TAI and sorafenib cohorts was not significant (5.8 *vs.* 2.3 months, $P=0.219$). The median PFS in the matched TAI cohort was significantly longer than the TACE cohort (6.5 *vs.* 2.8 months, $P<0.001$). The objective response rate (ORR) in the matched TAI cohort was significantly higher than the sorafenib cohort (36.4% *vs.* 0.0%, $P<0.001$) and the TACE cohort (48.7% *vs.* 4.7%, $P<0.001$). The incidences of adverse events (AEs) were similar among these three cohorts.

Conclusions: TAI with FOLFOX regimen was an effective and safe therapy that improved survival of patients with BCLC stage C HCC.

Keywords: Hepatocellular carcinoma (HCC); transarterial infusion chemotherapy; sorafenib; transarterial chemoembolization; FOLFOX

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Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death globally (1). Approximately up to over 60% of HCC patients were diagnosed at a BCLC stage C on first diagnosis (2,3). The median overall survival (OS) for these patients was only 2.0–7.9 months (4–7). Currently, the recommended treatment for these patients is sorafenib (4,5,8). However, low objective response rates, modest effectiveness, and high costs limit wide application of sorafenib in clinical practice (4,5,7,9). In Asian countries, transarterial chemoembolization (TACE) is widely used for BCLC stage C HCC patients (10–14). TACE is not recommended for patients with distant metastasis (8,15), and it should be used with caution in patients with poor liver function and in patients with main portal vein tumor thrombosis (PVTT) (16).

Recently, several studies showed transarterial infusion chemotherapy (TAI) with FOLFOX regimen alone or accompanied with sorafenib resulted in improved survival in BCLC stage C HCC patients (17,18). However, the role of TAI in treatment of advanced HCC patients is still unclear when compared with the standard and more commonly used sorafenib and TACE. Herein, a multi-center propensity score-matched analysis was conducted to compare the treatment effectiveness and safety of TAI with FOLFOX regimen compared to transarterial chemoembolization (TACE), and sorafenib in patients with BCLC stage C hepatocellular carcinoma (HCC). We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/hbsn.2020.03.14>).

Methods

Patients

The present study involved consecutive patients with BCLC stage C HCC treated at 3 hospitals in China (Table S1) between January 2015 to December 2018. The HCC diagnosis was made using the AASLD practice guidelines (19). The inclusion criteria were patients: (I) with Child-Pugh A or B liver function with adequate general condition; (II) who received a single treatment until radiologic response evaluation; (III) had at least one measurable lesion using the modified Response Evaluation Criteria on Solid Tumors (mRECIST) before treatment (20). Patients were excluded if they had: (I) a Child-Pugh score of C; (II) a Eastern Cooperative Oncology Group-performance score (ECOG-PS) >2; (III) no measurable lesion or radiology examination

before treatment, and (IV) a second malignancy. Details of patients' enrollment are shown in Figure 1.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Sun Yat-sen University Cancer Center (No. B2018-126-01). Informed consent was obtained from each patient for the data to be used for research.

Treatment procedures

The treatments using sorafenib, TACE, and TAI were similar to those previously reported (10,17,18). In TAI group, femoral artery puncture was performed using Seldinger's technique and catheterization was performed as routine. The TAI regimen comprised of oxaliplatin, 135 mg/m², from hour 0 to 3 on day 1, leucovorin, 400 mg/m², from hour 3 to 4.5 on day 1, fluorouracil, 400 mg/m², from hour 4.5 to 6.5 on day 1, and fluorouracil, 2,400 mg/m², over 46 hours from day 1 to 3. After infusion chemotherapy was completed, the catheter and sheath were removed. TAI was performed repetitively once every 3 to 4 weeks. Any implanted port system was not applied. The regimen of TACE comprised of one to three of the following drugs: platinum, anthracycline, antibiotics, and fluorouracil, which were mixed with lipiodol.

Follow-up and assessment

Each follow-up session included a history taking, physical examination, laboratory tests, and contrast enhanced computed tomography (CT) or/and magnetic resonance imaging (MRI) examination. The initial follow-up was 1 month after TACE, 6 to 8 weeks (2 cycles) after TAI or 2 months after sorafenib was given. The primary endpoint was overall survival (OS), which was the time from treatment (TAI, TACE, or sorafenib) until death from any cause. The secondary endpoints included progression-free survival (PFS), tumor response rate, post-progression survival (PPS), and treatment safety. PFS was defined as the time from treatment until disease progression or death, whichever came first. Tumor response rate included objective response rate (ORR) and disease control rate (DCR). ORR was defined as the percentage of complete response (CR) and partial response (PR) which was maintained for at least 4 weeks from the first radiological confirmation. DCR was defined as the ORR plus the percentage of patients with stable disease (SD). PPS was

Figure 1 Flow chart of the study. SYSUCC, Sun Yat-Sen University Cancer Center; GPPH, Guangdong Provincial People's Hospital; SMUNH, Southern Medical University Nanfang Hospital.

the time from disease progression to death from any cause. Tumor response was evaluated according to the mRECIST criteria. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (21). This study was censored on May 15, 2019.

The criteria for treatment discontinuation or switch included death, refusal by patients to continue treatment, intolerable toxicities, symptomatic or radiological progression, and enough tumor-down staging to undergo a potentially radical treatment such as liver resection, liver transplantation, ablation, or stereotactic body radiotherapy (SBRT).

Statistical analysis

Categorical variables were compared using the Pearson's χ^2 test or Fisher's exact test. Variable distributions were described using the mean $\pm$ standard error (SE) for normally distributed values, and medium and range for non-normally distributed values. Continuous variables were compared using the Student's *t*-test for normally distributed values or the Mann-Whitney test for skewed distributed values. Survival analyses were performed using the Kaplan-Meier method, and differences in the survival curves were analyzed using the log-rank test. A two-tailed $P < 0.05$ was considered statistically significant. The propensity-score model included gender (male or female), age ($\leq$ or > 50 years), Child-Pugh score before treatment (A or B), serum alpha-fetoprotein (AFP) level before treatment ($\leq$ or > 400 ng/mL), maximum diameter of tumor ($\leq$ or > 10 cm), tumor numbers (single or multiple), hemiliver involvement (unilateral or bilateral), macrovascular invasion (absent or

present), and distant metastasis (absent or present). Patients who received sorafenib and TAI, and TAI and TACE were matched in the ratio of 1:1, with the nearest neighbor caliper of a width of 0.2. All data analyses were performed using the SPSS software, version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

All patients

Between January 2015 to December 2018, the data of 457 patients (418 men and 39 women; median age, 53 years, range, 18–91 years) who were included into this study during the study period, 95, 273, and 89 underwent TAI, TACE, or sorafenib, respectively (Table S1 and Figure 1). The clinical characteristics of the entire study cohort are shown in Table 1. The ORR of patients treated in the TAI, TACE, and sorafenib groups were 44.3%, 7.7%, and 1.3%, respectively. The ORR of patients who underwent TAI was significantly higher than those who received TACE ($P < 0.001$) and sorafenib ($P < 0.001$). In addition, the ORR of patients who underwent TACE was significantly higher than those who received sorafenib ($P = 0.035$). The DCR of patients treated with TAI, TACE, and sorafenib were 65.9%, 57.6%, and 53.8%, respectively. There were no significant differences among these 3 treatment groups (TAI *vs.* TACE, $P = 0.166$; TAI *vs.* sorafenib, $P = 0.108$; sorafenib *vs.* TACE, $P = 0.545$).

The median follow-up time was 6.8 months (range, 0.2 to 52.5 months). On follow-up, 34, 202, and 50 patients treated with TAI, TACE, and sorafenib, respectively, had died; and the corresponding 55, 188, and 56 patients, respectively, had developed disease progression. The

Table 1 Clinical characteristics of the entire cohort of patients

	TAI (n=95)	TACE (n=273)	Sorafenib (n=89)	P value (TAI vs. TACE)	P value (TAI vs. sorafenib)
Age (years)	48.6±1.2	53.3±0.7	52 (25–77)	0.001	0.170
Gender				0.022	0.082
Male	81 (85.3%)	254 (93.0%)	83 (93.3%)		
Female	14 (14.7%)	19 (7.0%)	6 (6.7%)		
Serum biomarkers before treatment					
AFP (ng/mL)	2,660.0 (1.14–128,350)	4,836.5 (1.91–121,000)	871.25 (1.34–121,000)	0.119	0.399
ALB (g/L)	41.2 (24.1–49.8)	41.3 (25.0–46.5)	40.2 (15.0–48.7)	0.893	0.038
TBil (μmol/L)	14.9 (6.3–206.0)	19.3 (4.1–154.7)	17.7 (4.3–74.2)	0.000	0.003
PT (s)	12.3±0.1	12.6 (6.0–136.0)	12.9 (10.5–33.0)	0.036	0.004
Child-Pugh score before treatment				0.000	0.019
A	92 (96.8%)	192 (70.3%)	78 (87.6%)		
B	3 (3.2%)	81 (29.7%)	11 (12.4%)		
Maximum tumor diameter	9.8±0.4	9.4 (0.3–25.7)	8.5 (0.0–37.4)	0.315	0.006
No. of tumors				0.979	0.125
Single	38 (40.0%)	102 (40.2%)	26 (29.2%)		
Multiple	57 (60.0%)	152 (59.8%)	63 (70.8%)		
Tumor distribution				0.883	0.410
Uni-lobe	58 (61.1%)	169 (61.9%)	49 (55.1%)		
Bi-lobe	37 (38.9%)	104 (38.1%)	40 (44.9%)		
Macrovascular invasion				0.035	0.000
Absent	5 (5.3%)	36 (13.2%)	31 (34.8%)		
Present	90 (94.7%)	237 (86.8%)	58 (65.2%)		
Distant metastasis				0.582	0.000
Absent	77 (81.1%)	214 (78.4%)	45 (50.6%)		
Present	18 (18.9%)	59 (21.6%)	44 (49.4%)		
Tumor response [#]				0.000	0.000
CR/pCR	8 (9.1%)*	3 (1.1%)	0 (0.0%)		
PR	31 (35.2%)	18 (6.6%)	1 (1.3%)		
SD	19 (21.6%)	135 (49.8%)	42 (52.5%)		
PD	30 (34.1%)	115 (42.4%)	37 (46.3%)		
NA	7	2	9		
Pattern of progression after study treatment discontinuation				0.063	0.162
Intrahepatic lesion	14	71	22		
Vascular invasion	4	51	11		
Extrahepatic lesion	16	54	13		

Table 1 (continued)

Table 1 (continued)

	TAI (n=95)	TACE (n=273)	Sorafenib (n=89)	P value (TAI vs. TACE)	P value (TAI vs. sorafenib)
Pattern of progression when initial progression observed				0.002	0.066
Intrahepatic lesion	28	118	33		
Vascular invasion	6	82	16		
Extrahepatic lesion	30	85	23		

*, including 4 cases of CR and 4 cases of pCR; #, TAI (n=88), TACE (n=271), sorafenib (n=80).

Figure 2 Survival analysis of patients from the entire cohort treated with TAI, TACE, and sorafenib. (A) OS of all patients. (B) PFS of all patients. (C) PPS of all patients.

median OS of patients treated with TAI, TACE, and sorafenib were 27.8 (estimated), 7.1 (95% CI, 6.3–7.9), and 7.4 (95% CI, 5.8–9.1) months, respectively. The median OS of patients who underwent TAI was significantly longer than those treated with TACE ($P<0.001$) and sorafenib ($P<0.001$). The median PFS of patients treated with TAI, TACE, and sorafenib were 6.6 (95% CI, 5.0–8.2), 2.8 (95% CI, 2.4–3.2), and 3.2 (95% CI, 1.9–4.6) months, respectively. The median PFS of patients treated with TAI was significantly longer than those who were treated with TACE ($P<0.001$) and sorafenib ($P=0.001$). The median PPS of patients treated with TAI, TACE, and sorafenib were 15.5 (estimated), 4.1 (95% CI, 3.3–4.9), and 4.3 (95% CI, 2.8–5.7) months, respectively. The median PPS of patients treated with TAI was significantly longer than those who were treated with TACE ($P<0.001$) and sorafenib ($P<0.001$). The median OS, PFS, and PPS between patients who were treated with TACE and sorafenib were not significantly different ($P=0.754$, 0.341 , and 0.809 , respectively) (Table S2 and Figure 2).

Matched sorafenib and TAI groups

Propensity-score matching was carried out on 47 patients in each of the sorafenib and TAI groups. The median daily dose of sorafenib was 655 mg (296–800 mg) and the median duration of medication was 69 days (20–1,101 days). The median number of cycles for TAI was 4 (1–6 cycles). The clinical characteristics of these 2 groups of patients are shown in Table 2.

The ORR of patients treated with TAI was significantly higher than those treated with sorafenib (36.4% *vs.* 0.0%, $P<0.001$), while the DCR between these two groups was not significantly different (TAI *vs.* sorafenib group, 63.6% *vs.* 47.7%, $P=0.133$). The median OS of patients in the TAI group (19.6 months, 95% CI, 12.5–26.7 months) was significantly longer than those in the sorafenib group (7.5 months, 95% CI, 4.5–10.4 months) ($P=0.009$). The median PFS between the sorafenib (2.3 months, 95% CI, 1.9–2.7 months) and TAI (5.8 months, 95% CI, 4.4–7.2 months) groups was not significantly different

Table 2 Clinical characteristics of the matched sorafenib and TAI groups

	Sorafenib (n=47)	TAI (n=47)	P value
Age (years)	51.6±2.5	52 (25–78)	0.958
Gender			0.267
Male	45 (95.7%)	41 (87.2%)	
Female	2 (4.3%)	6 (12.8%)	
Previous anti-tumor treatment			0.000
Absent	10 (21.3%)	40 (85.1%)	
Present	37 (78.7%)	7 (14.9%)	
Previous radical anti-tumor treatment			0.267
Absent	41 (87.2%)	45 (95.7%)	
Present	6 (12.8%)	2 (4.3%)	
Serum biomarker before treatment			
AFP			0.098
≤400 ng/mL	18 (38.3%)	26 (55.3%)	
>400 ng/mL	29 (61.7%)	21 (44.7%)	
WBC (×10 ⁹ /L)	6.3±0.4	5.9 (2.0–15.0)	0.982
NE (×10 ⁹ /L)	4.0 (1.1–10.3)	4.1 (1.2–13.1)	0.762
Hgb (g/L)	135.9±3.2	145.3±3.9	0.037
PLT (×10 ⁹ /L)	152 (10.7–512)	237 (72–664)	0.001
ALT (U/L)	51 (13.8–220.6)	44.8 (10.2–170.8)	0.871
ALB (g/L)	40.4±0.8	40.9 (24.1–48.6)	0.667
TBil (μmol/L)	17.5 (7.2–38.3)	14.8 (5.2–33.8)	0.055
PT (s)	12.8 (10.7–16.3)	12.1 (10.2–18.1)	0.479
CRE (μmol/L)	70.0±2.9	74.2 (38.1–194.6)	0.291
Child-Pugh score before treatment			1.000
A	44 (93.6%)	44 (93.6%)	
B	3 (6.4%)	3 (6.4%)	
Maximum diameter of tumor	7.7±0.8	9.8±0.5	0.084
Tumor numbers			1.000
Single	9 (19.1%)	9 (19.1%)	
Multiple	38 (80.9%)	38 (80.9%)	
Tumor distribution			1.000
Uni-lobe	23 (48.9%)	23 (48.9%)	
Bi-lobe	24 (51.1%)	24 (51.1%)	
Macrovascular invasion			0.712
Absent	3 (6.4%)	5 (10.6%)	

Table 2 (continued)

Table 2 (continued)

	Sorafenib (n=47)	TAI (n=47)	P value
Present	44 (93.6%)	42 (89.4%)	
Macrovascular invasion grade*			0.318
Vp1	0 (0%)	1 (2.4%)	
Vp2	6 (13.6%)	11 (26.2%)	
Vp3	21 (47.7%)	18 (42.9%)	
Vp4	17 (38.6%)	12 (28.6%)	
Distant metastasis			1.000
Absent	35 (74.5%)	35 (74.5%)	
Present	12 (25.5%)	12 (25.5%)	
Tumor response**			0.000
CR	0 (0%)	2 (4.5%)	
PR	0 (0%)	14 (31.8%)	
SD	21 (47.7%)	12 (27.3%)	
PD	23 (52.3%)	16 (36.4%)	
NA	3	3	
Pattern of progression when target treatment discontinued			0.100
Intrahepatic lesion	16	8	
Vascular invasion	8	1	
Extrahepatic lesion	8	9	
Serum biomarker after treatment			
AFP***			0.014
≤400 ng/mL	15 (37.5%)	30 (63.8%)	
>400 ng/mL	25 (62.5%)	17 (36.2%)	
NA	7	0	
WBC (×10 ⁹ /L)	8.0 (2.2–17.9)	5.0 (2.8–12.8)	0.000
NE (×10 ⁹ /L)	5.4 (0.8–16.4)	3.0 (0.9–11.3)	0.000
Hgb (g/L)	135.9±4.8	138.0 (48.0–188.0)	0.673
PLT (×10 ⁹ /L)	170.8±14.7	148.0 (42.0–444.0)	0.812
ALT (U/L)	41.9 (17.1–274.0)	19.4 (7.3–202.3)	0.000
ALB (g/L)	39.0±1.1	40.4 (22.5–47.7)	0.425
TBil (μmol/L)	23.1 (8.2–251.6)	11.8 (4.5–96.4)	0.000
PT (s)	12.7 (9.8–48.5)	11.6±0.2	0.000
CRE (μmol/L)	66.5±2.4	65.4 (34.2–279.7)	0.970

Table 2 (continued)

Table 2 (continued)

	Sorafenib (n=47)	TAI (n=47)	P value
Child-Pugh score after treatment****			0.017
A	28 (71.8%)	44 (93.6%)	
B	8 (20.5%)	3 (6.4%)	
C	3 (7.7%)	0 (0%)	
NA	8	0	
Follow-up treatment			0.052
Absent	35 (74.5%)	26 (55.3%)	
Present	12 (25.5%)	21 (44.7%)	
Follow-up potential radical treatment			0.000
Absent	46 (97.9%)	33 (70.2%)	
Present	1 (2.1%)	14 (29.8%)	
Follow-up surgery			0.000
Absent	47 (100.0%)	35 (74.5%)	
Present	0 (0.0%)	12 (25.5%)	
Pattern of progression when initial progression observed			0.032
Intrahepatic lesion	22	18	
Vascular invasion	11	3	
Extrahepatic lesion	10	18	

*, sorafenib (n=44), TAI (n=42); **, sorafenib (n=44), TAI (n=44); ***, sorafenib (n=40), TAI (n=47); ****, sorafenib (n=39), TAI (n=47).

Figure 3 Survival analysis of patients from the matched sorafenib and TAI groups. (A) OS of matched sorafenib and TAI groups. (B) PFS of matched sorafenib and TAI groups. (C) PPS of matched sorafenib and TAI groups.

($P=0.219$). For the 33 patients in the sorafenib group and 32 patients in the TAI group included in the PPS analysis, the median PPS of patients treated with TAI (unreached) was significantly longer than those treated with sorafenib (4.1 months, 95% CI, 2.5–5.8 months) ($P=0.013$; Figure 3).

After the pattern of disease progression was classified into

three categories (intrahepatic lesion, vascular invasion, and extrahepatic lesion), PPS analysis showed that there were no significant differences between the TAI and sorafenib group in all these three patterns (Tables S3,S4).

Univariate and multivariate Cox regression analyses for OS and PFS showed grade Vp4 macrovascular invasion,

presence of distant metastasis, AFP >400 ng/mL after treatment, and absence of potential salvage radical treatment after tumor-downstaging were independent prognostic indicators of OS. The presence of distant metastasis, AFP >400 ng/mL after treatment and PT >13.5 seconds after treatment were independent prognostic indicators of PFS in the matched sorafenib and TAI groups (Tables S5,S6).

The overall incidences of AEs were similar between the matched sorafenib and TAI groups ($P=0.229$; Table S7). Leukocytopenia, neutropenia, pain, vomiting, and anorexia were more frequently found in the TAI group: ($P=0.012$, 0.032 , 0.006 , <0.001 , and 0.046 , respectively), while hand-foot skin reaction (HFSR), diarrhea, hyperbilirubinemia, and prolonged prothrombin time (PT) ($P=0.000$, 0.021 , 0.002 , and 0.019 , respectively) were more frequently found in the sorafenib group. Hypoalbuminemia, hyperbilirubinemia, anemia, pain, thrombocytopenia, and

anorexia were common ($>10\%$) in both groups.

Matched TAI and TACE groups

After propensity-score matching, there were 85 patients in each of the TAI and TACE groups. The median number of cycles for the TAI and TACE groups were 4 (1–6 cycles) and 1 (1–4 cycles), respectively. The clinical characteristics of the two groups are shown in Table 3.

The ORR of patients in the TAI group was significantly higher than those from the TACE group (48.7% vs. 4.7% , $P<0.001$), while the DCR between these two groups showed no significant difference (TAI vs. TACE, 65.4% vs. 56.5% , $P=0.244$). The median OS and PFS of the TAI group were significantly longer than the TACE groups (OS, 27.8 months, estimated, vs. 6.6 months, 95% CI, 5.3–7.9 months; PFS, 6.5 months, 95% CI, 4.6–8.4 months

Table 3 Clinical characteristics of matched TAI and TACE groups

	TAI (n=85)	TACE (n=85)	P value
Age (yr)	49.3±1.2	49 [32–74]	0.546
Gender			1.000
Male	77 (90.6%)	76 (89.4%)	
Female	8 (9.4%)	9 (10.6%)	
Previous anti-tumor treatment			0.794
Absent	78 (91.8%)	76 (89.4%)	
Present	7 (8.2%)	9 (10.6%)	
Previous radical anti-tumor treatment			0.099
Absent	83 (97.6%)	77 (90.6%)	
Present	2 (2.4%)	8 (9.4%)	
Serum biomarker before treatment			
AFP			0.128
≤400 ng/mL	29 (34.1%)	20 (23.5%)	
>400 ng/mL	56 (65.9%)	65 (76.5%)	
WBC ($\times 10^9/L$)	6.2 (2.0–15.0)	6.4±0.3	0.993
NE ($\times 10^9/L$)	4.1 (1.2–13.1)	4.1±0.3	0.740
Hgb (g/L)	148.4±2.6	145.3±2.4	0.376
PLT ($\times 10^9/L$)	219.0 (72.0–664.0)	240.6±14.8	0.926
ALT (U/L)	44.6 (7.7–291.4)	39.9 (18.4–304.9)	0.270
ALB (g/L)	41.1 (24.1–49.8)	41.2±0.6	0.608

Table 3 (continued)

Table 3 (continued)

	TAI (n=85)	TACE (n=85)	P value
TBil (μmol/L)	15.0 (5.2–32.6)	14.9 (5.8–36.0)	0.042
PT (s)	12.3±0.1	12.8±0.3	0.136
CRE (μmol/L)	73.9 (41.9–194.6)	70.9±2.6	0.510
Child-Pugh score before treatment			1.000
A	83 (97.6%)	82 (96.5%)	
B	2 (2.4%)	3 (3.5%)	
Maximum diameter of tumor (cm)	9.5±0.4	11.8 (1.0–16.2)	0.084
Tumor numbers			0.536
Single	34 (40.0%)	39 (45.9%)	
Multiple	51 (60.0%)	46 (54.1%)	
Tumor distribution			0.249
Uni-lobe	54 (63.5%)	62 (72.9%)	
Bi-lobe	31 (36.5%)	23 (27.1%)	
Macrovascular invasion			0.188
Absent	5 (5.9%)	11 (12.9%)	
Present	80 (94.1%)	74 (87.1%)	
Macrovascular invasion grade [#]			0.903
Vp1	3 (3.8%)	3 (4.1%)	
Vp2	22 (27.5%)	22 (29.7%)	
Vp3	33 (41.3%)	26 (35.1%)	
Vp4	22 (27.5%)	23 (31.1%)	
Distant metastasis			0.348
Absent	70 (82.4%)	64 (75.3%)	
Present	15 (17.6%)	21 (24.7%)	
Cycles	4 [1–6]	1 [1–4]	0.000
Tumor response ^{##}			0.000
CR (and pCR)	8* (10.3%)	1 (1.2%)	
PR	30 (38.5%)	3 (3.5%)	
SD	13 (16.7%)	44 (51.8%)	
PD	27 (34.6%)	37 (43.5%)	
NA	7	0	
Pattern of progression when target treatment discontinued			0.135
Intrahepatic lesion	12	21	
Vascular invasion	4	18	

Table 3 (continued)

Table 3 (continued)

	TAI (n=85)	TACE (n=85)	P value
Extrahepatic lesion	15	19	
Serum biomarker after treatment			
AFP ^{###}			0.000
≤400 ng/mL	44 (51.8%)	15 (21.4%)	
>400 ng/mL	41 (48.2%)	55 (78.6%)	
NA	0	15	
WBC (×10 ⁹ /L)	4.9 (2.3–12.8)	6.7 (3.5–16.9)	0.000
NE (×10 ⁹ /L)	3.0 (0.4–11.3)	3.9 (2.1–16.1)	0.000
Hgb (g/L)	138.5 (48.0–188.0)	129.9±3.1	0.156
PLT (×10 ⁹ /L)	151.0 (42.0–444.0)	208.1±13.1	0.000
ALT (U/L)	18.9 (5.9–202.3)	42.7 (9.0–1,776.8)	0.000
ALB (g/L)	40.0 (22.5–47.1)	38.3±0.7	0.360
TBil (μmol/L)	12.5 (5.2–96.4)	15.4 (3.9–155.6)	0.004
PT (s)	11.8±0.1	12.6 (11.3–17.3)	0.000
CRE (μmol/L)	66.2 (34.2–279.7)	65.6 (42.1–130.9)	0.597
Child-Pugh score after treatment ^{####}			0.168
A	80 (95.2%)	48 (87.3%)	
B	4 (4.8%)	7 (23.7%)	
NA	1	30	
Follow-up treatment			0.003
Absent	42 (49.4%)	62 (72.9%)	
Present	43 (50.6%)	23 (27.1%)	
Follow-up potential radical treatment			0.001
Absent	49 (57.6%)	69 (81.2%)	
Present	36 (42.4%)	16 (18.8%)	
Follow-up surgery			0.000
Absent	56 (65.9%)	82 (96.5%)	
Present	29 (34.1%)	3 (3.5%)	
Pattern of progression when initial progression observed			0.045
Intrahepatic lesion	24	33	
Vascular invasion	6	23	
Extrahepatic lesion	27	29	

*, including 4 cases of Pcr; #, TAI (n=80), TACE (n=74); ##, TAI (n=78), TACE (n=85); ###, TAI (n=85), TACE (n=70); ####, TAI (n=84), TACE (n=55).

Figure 4 Survival analysis of the matched TAI and TACE groups. (A) OS of matched TAI and TACE groups. (B) PFS of matched TAI and TACE groups. (C) PPS of matched TAI and TACE groups.

vs. 2.8 months, 95% CI, 2.0–3.6 months; both $P < 0.001$). On PPS analysis for the 48 patients in the TAI group and 55 patients in the TACE group, the median PPS of the TAI group (13.9 months, 95% CI, 9.7–18.1 months) was significantly longer than the TACE group (4.0 months, 95% CI, 3.6–4.3 months; $P < 0.001$; Figure 4). Furthermore, analysis of the progression patterns showed the median PPS of the TAI group was significantly longer than the TACE group in patients having intrahepatic lesions and macrovascular invasion progression (Tables S8,S9).

Univariate and multivariate analyses for OS and PFS showed that CRE >100 $\mu\text{mol/L}$ before treatment, CRE >100 $\mu\text{mol/L}$ after treatment, and absence of potentially curative treatment after tumor-downstage were independent prognostic indicators of OS; and AFP >400 ng/mL before treatment, AFP >400 ng/mL after treatment, AFP level not decrease after treatment, PT >13.5 seconds after treatment, and absence of potentially curative treatment after tumor-downstage were independent prognostic indicators of PFS in the matched TAI and TACE groups (Tables S10,S11).

The treatment-related AEs are shown in Table S12. The overall incidences of AEs were similar between the matched TAI and TACE groups ($P = 0.280$). The following AEs were more frequently found in the TAI group: leukocytopenia, neutropenia, and dysuria ($P = 0.001$, <0.001 , 0.006, and 0.029, respectively). The following AEs were more frequently found in the TACE group: elevated ALT level and fever ($P = 0.002$ and <0.001 , respectively). Hypoalbuminemia, pain, vomiting, hyperbilirubinemia, anemia, thrombocytopenia, prolonged PT and anorexia were common ($>10\%$) in the two groups.

Discussion

Sorafenib and TACE have been recommended as the standard

and the most commonly performed treatments for BCLC stage C HCC patients (4,5,8,10–12). However, limitations hampered their routine use in real-world clinical practice and an effective alternative therapy is urgently required.

The effectiveness of TAI to treat advanced HCC patients who were unable to receive TACE and percutaneous ethanol injection (PEI) was reported in 1995 by Toyoda *et al.* using the regimen containing cisplatin and fluorouracil. These authors reported a 1-year OS rate of 61.1% (22). Thereafter, TAI using cisplatin, fluorouracil and with or without interferon became accepted as a common therapy to treat advanced HCC patients in Japan and Korea. However, the median overall survival was still unsatisfactory which was reported to vary between 5.3–14.0 months (23–26). The FOLFOX regimen delivered by systemic and hepatic arterial routes (27,28) is commonly used in patients with colorectal cancer with liver metastasis. Several studies showed the FOLFOX regimen is also effective in patients with advanced HCC (17,18,29).

For the entire cohort in the present study, the median OS, PFS and PPS, as well as the ORR and CR rate for the patients treated with TAI (44.3% and 9.1%, respectively) were significantly longer than those treated with TACE and sorafenib. In addition, 4 patients in the TAI group achieved complete pathological CR (PCR). However, the baseline clinical characteristics among the groups were unbalanced. The proportion of patients with multiple lesions and distant metastasis were highest in the sorafenib group, and the liver function of patients treated with TACE was the worst according to the Child-Pugh scoring. A propensity-score match analysis was therefore performed to reduce biases (30). The baseline tumor and prognosis related factors before treatment became comparable in the matched groups after the matching.

One of the most important findings of the present study was that the median OS of the matched TAI group was significantly longer than the sorafenib (19.6 *vs.* 7.5 months, $P=0.009$) and TACE (27.8 *vs.* 6.6 months, $P<0.001$) groups. This result suggested that patients treated with TAI using the FOLFOX regimen was the best treatment for BCLC stage C HCC patients. The median PFS of the matched TAI group was significantly longer than the TACE group (6.5 *vs.* 2.8 months, $P<0.001$), suggesting that TAI using the FOLFOX regimen resulted in better local lesion control than TACE. On the other hand, as the median PFS between the matched TAI and sorafenib groups (5.8 *vs.* 2.3 months, $P=0.219$) were not significantly different, further suggesting that for advanced HCC patients, a combination of local and systemic treatments may be required to control both intra- and extra-hepatic lesions. Also, the median PPS of the matched TAI was significantly longer, which could be attributed to the smaller damage for liver function TAI made. Even if after the tumor progression, there were still more available alternative treatments, which could bring better survival.

Tumor response after TAI treatment was satisfactory in this study. The ORR was about 40% in the matched TAI group. There was even a CR rate of around 5–10% in the two matched TAI groups. A high tumor response rate brings a higher chance for potentially radical treatments, such as liver resection, transplantation and local ablative therapy with a possibility of long-term survival for advanced HCC patients (31–33). As our multidisciplinary treatment (MDT) group is led by surgeons, there is an increased awareness of the group to grasp the narrow time window for patients who could be downstaged. This explains why the proportion of patients who underwent surgery in this study was higher, and the median OS was longer than the previously reported studies on TAI using the FOLFOX regimen (17,18). Several factors were identified as independent prognostic indicators of OS and PFS in both matched groups. It should be noted that AFP >400 ng/mL, PT >13.5 seconds, and absence of potentially curative treatment after tumor-downstage were important factors in both matched groups, suggesting that these factors were highly correlated with prognosis in advanced HCC patients. The results also showed that in the real world, for carefully selected patients with good liver function and light tumor burden, potentially curative treatment such as surgical resection could bring significant benefits for survival and disease control.

Safety analysis showed that TAI was safe for advanced HCC patients with an AEs incidence which was comparable

to that of the treatments using sorafenib and TACE ($P=0.229$ and 0.280, respectively). Specifically, myelosuppression and gastrointestinal symptoms were more frequent and severe in patients treated with TAI. However, these AEs were reversible and easily manageable in clinical practice. The real concern was damage to liver function which happened slightly more often in patients treated with TAI than with other treatments. It has been shown that decompensated liver function was more important than distant metastasis in affecting long-term prognosis in patients with advanced HCC (34). Patients with good liver function have good compliance to treatment, good quality of life, and a better chance to receive alternative and effective treatments even with disease progression, thus contributing to the better survival.

The difference between the present study and the previously reported studies is on a technical point. While in our study arterial catheterization was performed in every cycle rather than using an implanted port system (24–26,35). Our approach has the benefits of better targeting tumor-feeding arteries for infusion chemotherapy, which can also be adjusted based on changes in the blood supply to tumors, thus allowing a higher local drug concentration, better pertinence, and flexibility. A treatment interval of 3–4 weeks was implemented in this study, which provided continuity of anti-tumor effects by cytotoxic agents and an enough time interval for the patients to recover liver and body functions. Also, Oxaliplatin kills cancer cells and induces immunogenic tumor cell death in a different way from cisplatin (36,37).

There are limitations of this study. First, this is a retrospective study with its inherent biases despite the use of propensity-score match analysis. Second, the short follow-up might affect firm final conclusions that can be drawn from the results of this study (38). More prospective randomized controlled clinical trials on TAI, with or without other combination therapies are needed to further define the role that TAI actually plays in the treatment of patients with BCLC stage C hepatocellular carcinoma.

Conclusions

TAI using the FOLFOX regimen was an effective and safe treatment for BCLC stage C HCC patients. However, the results need to be validated in future prospective randomized controlled clinical trials.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Sun Yat-sen University Cancer Center (No. B2018-126-01).

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