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FOLFOX-Based Hepatic Arterial Infusion Chemotherapy with Sequential Drug-Eluting Bead Transarterial Chemoembolization for Unresectable Large Hepatocellular Carcinoma: A Single-Center Retrospective Cohort Study

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Background: For patients with large unresectable hepatocellular carcinoma (HCC), the effectiveness of conventional transarterial chemoembolization (TACE) remains suboptimal, which necessitates the administration of substantial volumes of chemotherapy drugs and lipiodol, thereby increasing the risk of liver failure and other chemotherapy-related complications. Therefore, we devised a strategy of initial hepatic arterial infusion chemotherapy (HAIC) followed by sequential drug-eluting bead TACE (DEB-TACE). In our treatment design, a lower tumor burden after HAIC facilitated complete embolization of tumor vasculature, and the use of less amount of embolic agents reduced the incidence of liver failure and embolization syndromes.

Methods: This retrospective study evaluated consecutive patients with unresectable large HCC with a maximum tumor diameter of ≥7 cm who received FOLFOX-HAIC combined with sequential DEB-TACE from April 2019 to February 2024. Efficacy was evaluated using the objective response rate (ORR), overall survival (OS), and progression-free survival (PFS); and safety was assessed using the frequency of key adverse events (AEs).

Results: Among the 76 patients included, the median maximum tumor diameter was 12.4 cm (range, 7.0–23.4 cm). The overall ORRs based on mRECIST and RECIST 1.1 criteria were 94.1% and 51.5%, respectively. The median OS was 28.1 months (95% CI, 22.7–33.4), and the median PFS was 11.7 months (95% CI, 7.7–15.8). All patients experienced AEs, but only 18.4% experienced grade 3 or 4 AEs, there was no treatment-related mortality.

Conclusion: In this single-center, retrospective study, our results suggested that FOLFOX-HAIC with sequential DEB-TACE demonstrated promising efficacy and safety for patients with unresectable HCC with a maximum tumor diameter of ≥7 cm.

Keywords: large unresectable hepatocellular carcinoma, hepatic arterial infusion chemotherapy, drug-eluting bead transarterial chemoembolization, sequential

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and is the third leading cause of cancer-related deaths worldwide.[1] Approximately 80% of HCC cases worldwide are in developing countries,[2,3] where HCC

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surveillance is not widely applied. Consequently, most patients in these areas with the highest risk of HCC are initially diagnosed with large tumors.[4] However, most large HCC cases are not suitable candidates for surgical resection because of insufficient residual liver volume, insufficient surgical margins, or macrovascular invasion.[5]

The Barcelona Clinic Liver Cancer (BCLC) guidelines advocate the use of transarterial chemoembolization (TACE) as a therapeutic strategy for patients with unresectable HCC.[6] However, the effectiveness of TACE is often suboptimal in patients with large HCC tumors,[7,8] which have abundant extrahepatic collateral arteries, making it difficult to perform complete embolization. In addition, the use of a large amount of embolization agents may cause serious adverse events (SAEs), such as hepatic dysfunction, postembolization syndrome, and ectopic embolization.[9,10]

Hepatic arterial infusion chemotherapy (HAIC) exerts its antitumor effect through the continuous infusion of high concentrations of chemotherapeutic agents.[11] In recent years, several studies have demonstrated that HAIC with oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) significantly improved the survival of patients with advanced HCC.[12–14] Li et al reported that FOLFOX-HAIC had superior efficacy and safety to TACE for patients with large unresectable HCC.[13] Given that HAIC does not entail the use of an embolization agent, its SAEs were significantly lower than those of TACE.[9,10] In addition, HAIC combined with tyrosine kinase inhibitors (TKIs) and inhibitors of programmed cell death protein 1 (PD-1) or its ligand (PD-L1) has been shown to have a potential synergistic effect, with a remarkably high objective response rate (ORR) of up to 60% to 80% in HCC.[15–17]

However, despite several cycles of HAIC, residual HCC activity can persist because of the high heterogeneity of HCC cell sensitivity to chemotherapy. Therefore, for the treatment of large HCC, an ideal strategy would be initial HAIC administration to minimize tumor size followed by TACE to eliminate residual tumor activity. Unlike conventional TACE (cTACE), drug-eluting bead TACE (DEB-TACE) can increase the intensity and duration of tumor ischemic necrosis and deliver large amounts of chemotherapeutic agents to the tumor in a controlled and sustained manner.[18,19] In fact, compared with cTACE, DEB-TACE was reported to have higher ORR, longer progression-free survival (PFS), and better tolerability in large HCC cases.[20–23] To date, two studies have reported the use of simultaneous combination of DEB-TACE and FOLFOX-HAIC for advanced HCC,[24,25] but the strategy of initial FOLFOX-HAIC followed by sequential DEB-TACE has not been reported. Therefore, we conducted this retrospective study to evaluate the efficacy and safety of FOLFOX-HAIC with sequential DEB-TACE for the treatment of unresectable large HCC (≥7 cm).

Patients and Methods

This study was conducted according to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee (B2020-318-01) of Sun Yat-Sen University Cancer Center (SYSUCC; Guangzhou, China). Informed consent was obtained from all individual participants included in the study. Written informed consent was obtained from the patients for their anonymized information to be published in this article.

Patients

All patients with HCC who underwent FOLFOX-HAIC with sequential DEB-TACE between April 2019 and February 2024 at SYSUCC were retrospectively screened for eligibility. The inclusion criteria were as follows: (1) diagnosed as HCC according to the American Association for the Study of Liver Diseases practice guidelines,[26] (2) the largest lesion measured ≥7 cm per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1),[27] (3) assessed by at least two experienced liver surgeons as unsuitable for surgical resection, (4) age ≥18 years, (5) Child–Pugh class A and B (score ≤7) liver function, (6) no previous treatment for HCC, and (7) adequate hematologic and organ functions. Patients were excluded based on the following criteria: (1) previous antitumor treatment, (2) history of other malignant tumors, (3) incomplete medical information, and (4) lost to follow-up.

HAIC Procedure

HAIC was performed as described previously.[12] Briefly, a microcatheter was placed in the main feeding hepatic artery, and the following regimen was infused: 85 or 135 mg/m^2 oxaliplatin from hour 0 to 3 on day 1, 400 mg/m^2 leucovorin from hour 3 to 4.5 on day 1, 400 mg/m^2 5-fluorouracil bolus from hour 4.5 to 6.5 on day 1, and 2,400 mg/m^2 5-fluorouracil over 23 or 46 h from day 1 to day 2 or 3. After HAIC completion, the catheter and sheath were removed.

Instead of an implanted port catheter system, repeat femoral artery puncture and catheterization were performed in the next HAIC cycle. HAIC was repeated once every 3 weeks for up to eight cycles. In cases of severe hematologic and/or nonhematologic toxic reactions, the chemotherapeutic drugs needed dose adjustments or even discontinuation.[12]

Almost all patients received simultaneous systemic drugs, including antiangiogenic drugs and PD-1/PD-L1 inhibitors, as detailed in Supplemental Table 1.

DEB-TACE Procedure

In general, DEB-TACE was performed in cases with significant tumor regression after several cycles of HAIC. Significant tumor regression was defined as more than 30% to 50% reduction of the maximum diameter of the target lesion or of the area of tumor enhancement on computed tomography (CT)/magnetic resonance imaging (MRI) or digital subtraction angiography (DSA). In some patients who were unable to continue HAIC for various reasons, such as intolerable drug toxicity, DEB-TACE was performed to completely embolize the residual tumor even if the criteria for significant tumor regression were not met.

The drug-loaded microspheres (CalliSpheres®; Hengrui Medical, Suzhou, China) used for DEB-TACE measured 100–300 μm in diameter; each vial was loaded with 80 mg of epirubicin (Pfizer Pharmaceuticals, Wuxi, China) according to the standard formulation method.[28] After drug loading, an equal quantity of iodine contrast agent was added for injection. The puncture and catheterization methods for DEB-TACE and HAIC were the same. A 3.5-Fr catheter was inserted into the celiac trunk or superior mesenteric artery for arteriography, then a 2.6-Fr microcatheter was superselectively placed into the tumor-feeding arteries; a second radiography was performed to confirm placement.[29] During embolization, the DEB suspension was injected at a rate of 1–3 mL/min. Embolization was stopped when the contrast agent was retained in the tumor-feeding artery for 3–5 cardiac cycles. After a 5-min pause, the angiogram was repeated. If embolization was incomplete, sequential embolization with 100–300-μm diameter microspheres (Embosphere®; Merit Medical, Salt Lake City, USA) or iodized oil was performed until the endpoint was reached.[30] According to the fitness status and liver function score of the patient, on-demand TACE was performed in patients with residual lesions on repeat contrast-enhanced CT or MRI.

Data Collection

All clinical baseline characteristics of the eligible patients were collected from the medical records at SYSUCC; these included gender and age; Eastern Cooperative Oncology Group Performance Status (ECOG PS) score; Child–Pugh score, status of hepatitis virus infection, and presence of cirrhosis; tumor size, number, distribution, vascular invasion, lymph node (LN) metastasis, distant metastasis, and BCLC stage; and levels of alpha fetoprotein (AFP), white blood cells, neutrophils, hemoglobin, platelets, alanine transaminase (ALT), serum albumin, total bilirubin, prothrombin time, and creatinine.

Follow-Up and Survival Analyses

Each follow-up visit included medical history taking, physical examination, laboratory testing, and contrast-enhanced CT and/or MRI examination. The initial follow-up appointment was at 6–8 weeks (two HAIC cycles) after the first treatment. Patients were followed up until April 1, 2024.

Overall survival (OS) was defined as the interval from the date of initial HAIC to death from any cause. PFS was defined as the interval from the date of initial HAIC to tumor progression or death from any cause, whichever occurred first. ORR was defined as the proportion of patients who achieved either complete response (CR) or partial response (PR) for at least 4 weeks from the first radiological confirmation. The disease control rate (DCR) was defined as the ORR plus the percentage of patients with stable disease (SD). Tumor response was assessed using RECIST v1.1 and modified RECIST (mRECIST).[27,31] AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[27]

Statistical Analysis

Normally distributed variables were described as mean ± standard error, and nonnormally distributed variables were described as median and interquartile range (IQR). Categorical variables were compared using Pearson $\chi 2$ test or Fisher's exact test. Continuous parametric variables were compared using unpaired Student's *t*-test, whereas continuous nonparametric variables

were compared using Mann–Whitney *U*-test. The Kaplan–Meier method was used for survival analysis, and the Log rank test was used to compare survival curves. Forward logistic regression-based univariate and multivariate Cox regression analyses were used to identify the independent predictors of OS and PFS. A two-tailed p value of <0.05 was considered statistically significant. All data analyses were performed using SPSS software, version 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

Patient demographics and baseline characteristics are summarized in Table 1. Finally, this study included 76 patients (Figure 1) with a median age of 55 years (IQR, 45–60 years). Among all the patients, 70 are male and 6 are female. The median follow-up duration was 18.9 months (IQR, 11.8–23.5 months). Of the 76 patients, 53 (69.7%) and 23 (30.3%)

Table 1 Baseline Clinical Characteristics of the Patients (n = 76)

Characteristics	Patients
Gender	
Male	70 (92.1%)
Female	6 (7.9%)
Age	
Median (IQR)	55 (45–60)
≤50	28
>50	48
ECOG PS score	
0	53 (69.7%)
1	23 (30.3%)
Child–Pugh score	
5	62 (81.6%)
6	13 (17.1%)
7	1 (1.3%)
Etiology	
Hepatitis B	68 (89.5%)
Others	8 (10.5%)
Cirrhosis	
Absence	56 (73.4%)
Presence	20 (26.3%)
Tumor size, cm	
Median (IQR)	12.4 (9.5–15.0)
7–10	22 (28.9%)
10–15	36 (47.4%)
>15	18 (23.7%)

(*Continued*)

Table 1 (Continued).

Characteristics	Patients
Tumor number	
Solitary	26 (34.2%)
Multiple	50 (65.8%)
Tumor distribution	
Unilobar	33 (43.4%)
Bilobar	43 (56.6%)
Vascular invasion	
Absent	40 (52.6%)
Present	36 (47.4%)
LN metastasis	
Absent	57 (75.0%)
Present	19 (25.0%)
Distant metastasis	
Absent	61 (80.3%)
Present	15 (19.7%)
BCLC stage	
A	11 (14.5%)
B	17 (22.4%)
C	48 (63.1%)
AFP, ng/mL	
≤400	36 (47.4%)
>400	40 (52.6%)
WBC, median (IQR), $\times 10^9$/L	6.6 (5.5–8.4)
NE, median (IQR), $\times 10^9$/L	4.3 (3.2–5.3)
HGB, median (IQR), g/L	135.5 (125.3–145.8)
PLT, median (IQR), $\times 10^9$/L	248.0 (200.3–337.8)
ALT, median (IQR), U/L	49.8 (36.3–74.7)
ALB, median (IQR), g/L	41.3 (37.3–43.0)
TBIL, median (IQR), μmol/L	14.9 (10.5–21.2)
PT, median (IQR), seconds	12.0 (11.3–12.7)
CRE, median (IQR), μmol/L	71.5 (60.9–82.0)

Abbreviations: IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LN, lymph node; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; WBC, white blood cell; NE, neutrophil count; HGB, hemoglobin; PLT, platelet count; ALT, alanine transaminase; ALB, albumin; TBIL, total bilirubin; PT, prothrombin time; CRE, creatinine.

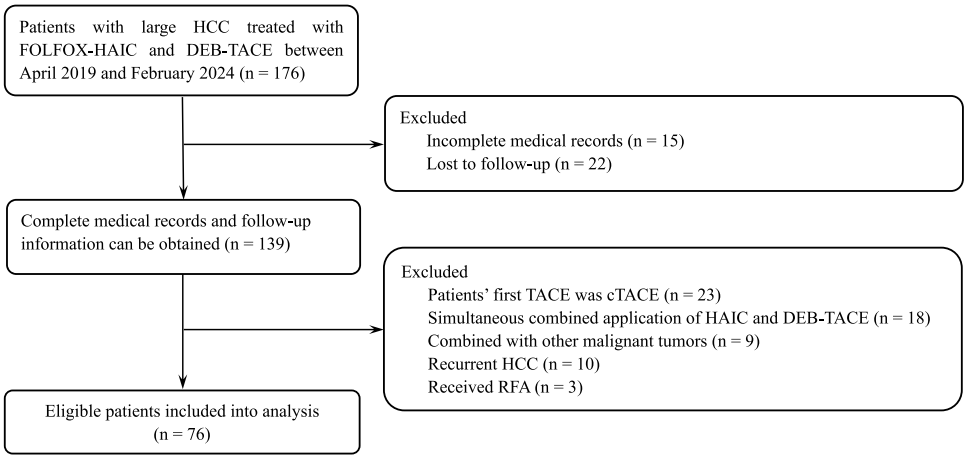

Figure 1 Flow diagram of patient enrollment.
Abbreviations: HCC, hepatocellular carcinoma; FOLFOX-HAIC, hepatic artery infusion chemotherapy with oxaliplatin, 5-fluorouracil, and leucovorin; TACE, transarterial chemoembolization; cTACE, conventional TACE; DEB-TACE, drug-eluting bead TACE; RFA, radiofrequency ablation.

had ECOG PS scores of 0 and 1, respectively, and 75 (98.7%) had Child–Pugh class A. The etiology of HCC was hepatitis B in 68 (89.5%) patients. The maximum tumor diameter was at a median of 12.4 cm (range, 7.0–23.4 cm) and was 7–10 cm in 22 (28.9%), 10–15 cm in 36 (47.4%), and >15 cm in 18 (23.7%). Among the 76 patients, 40 (52.6%) had AFP levels >400 ng/mL, 50 (65.8%) had multiple lesions, 36 (35.7%) had macrovascular invasion, 19 (25.0%) had hilar LN metastasis, and 15 (19.7%) had distant metastasis.

The details of the HAIC cycles and doses, number of DEB-TACE procedures, and concomitant systemic therapy are summarized in Supplemental Table 1. The median number of procedures was 4 cycles (IQR, 1–8) for HAIC and 1 (range, 1–4) for DEB-TACE. Of all the 76 patients, 66 (86.8%) received concomitant anti-angiogenic drugs, including Lenvatinib (n = 42), Bevacizumab (n = 12), Apatinib (n = 10), and Donafenib (n = 2). In addition, among all the patients, 66 (86.8%) received anti-PD-1 or anti-PD-L1 immunotherapy, including Sintilimab (n = 22), Tislelizumab (n = 10), Toripalimab (n =10), Camrelizumab (n = 9), Atezolizumab (n = 8), Durvalumab (n = 3), Pembrolizumab (n = 3), and Nivolumab (n = 1).

Treatment Efficacy

Tumor response outcomes are shown in Table 2, and changes in intrahepatic target lesion size are shown in Figure 2. Among the 76 patients, tumor response assessment to entire procedure or HAIC alone was evaluable in 68 and 75 patients, respectively. Evaluation of entire procedure (n = 68) revealed CR rate of 5.9% and ORR of 94.2% using mRECIST and ORR of 51.5% and DCR of 98.5% using RECIST v1.1. After treatment, three patients were successfully converted and underwent radical liver tumor resection, five patients received radiotherapy, and one patient received

Table 2 Best Observed Treatment Response

Characteristics	Entire Procedure (n = 68)		After HAIC, Before DEB-TACE (n = 75)	
	RECIST	mRECIST	RECIST	mRECIST
Complete response (CR)	0	4 (5.9%)	0	3 (4.0%)
Partial response (PR)	35 (51.5%)	60 (88.3%)	25 (33.4%)	49 (65.3%)
Stable disease (SD)	32 (47.0%)	2 (2.9%)	49 (65.3%)	21 (28.0%)
Progressive disease (PD)	1 (1.5%)	2 (2.9%)	1 (1.3%)	2 (2.7%)
Objective response rate (ORR)	51.5%	94.2%	33.4%	69.3%
Disease control rate (DCR)	98.5%	97.1%	98.7%	97.3%

Abbreviations: HAIC, hepatic artery infusion chemotherapy; DEB-TACE, drug-eluting bead transarterial chemoembolization; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST.

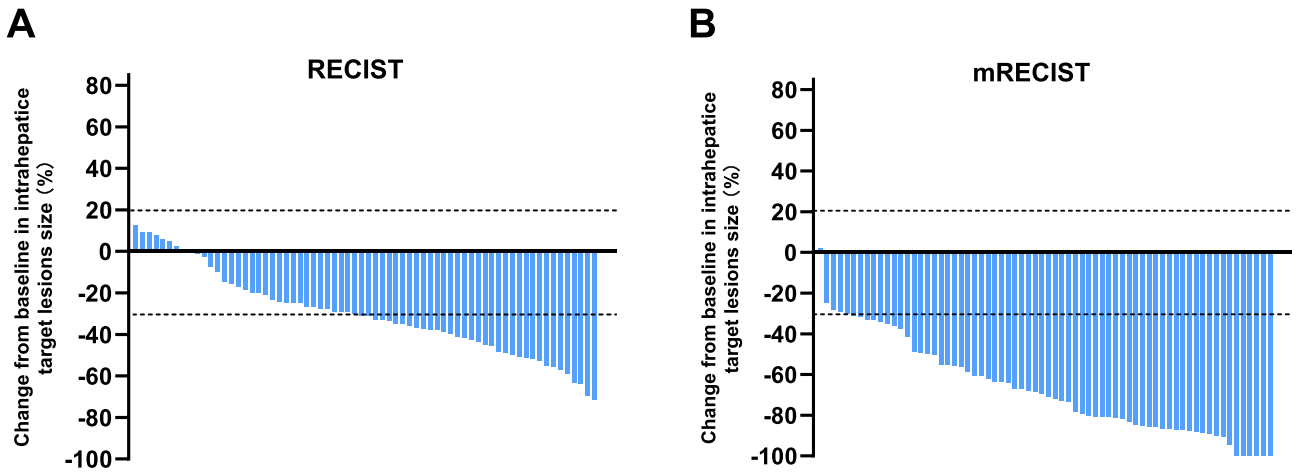

Figure 2 Best percent changes from baseline in the intrahepatic target lesion size after FOLFOX-HAIC combined with sequential DEB-TACE treatment. (**A**) according RECIST1.1 and (**B**) according to mRECIST criteria.

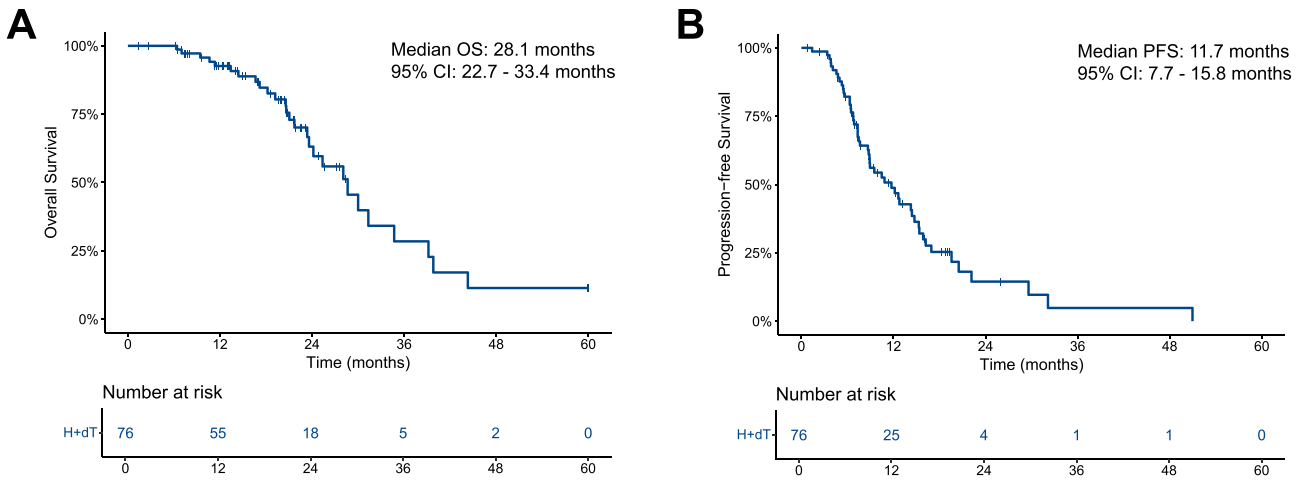

Figure 3 Kaplan–Meier curves of the patients (N = 76). (**A**) overall survival and (**B**) progression-free survival.

radiofrequency ablation (RFA). In an interim analysis after HAIC and before DEB-TACE, the ORR was 69.3% and the CR rate was 4.0% using mRECIST, whereas the ORR was 33.3% and the DCR was 98.7% using RECIST v1.1.

The 1-, 2-, and 3-year OS rates were 97.2%, 92.6%, and 84.7%, respectively, with a median OS of 28.1 months (95% CI, 22.7–33.4). The 1-, 2-, and 3-year PFS rates were 89.1%, 76.4%, and 64.2%, respectively, with a median PFS of 11.7 months (95% CI, 7.7–15.8, Figure 3). Table 3 presents the prognostic factors for OS and PFS. On univariate analysis, OS was significantly associated with distant metastasis (p = 0.002), tumor number (p = 0.022), tumor distribution (p = 0.013), number of DEB-TACE sessions (p = 0.033), and mRECIST tumor response to DEB-TACE (p = 0.027), and PFS was significantly associated with ECOG PS (p = 0.020), distant metastasis (p = 0.038), tumor number (p = 0.010), tumor distribution (p = 0.018), ALT level (p = 0.036), and mRECIST tumor response to DEB-TACE (p = 0.016). On multivariate Cox proportional analysis, mRECIST tumor response to DEB-TACE was a significant and independent predictor of OS (p = 0.032, HR = 0.348, 95% CI 0.136–0.887) and PFS (p = 0.006, HR = 0.386, 95% CI 0.197–0.759).

Safety

As shown in Table 4, the overall incidence of AEs was 96.1% after HAIC and 100% after HAIC with sequential DEB-TACE. There was no treatment-related mortality. For HAIC with sequential DEB-TACE, the most common AEs of any grade were

Table 3 Univariate and Multivariate Analyses of the Prognostic Factors for Overall Survival and Progression-Free Survival

Characteristics	Overall Survival						Progression-Free Survival					
	Univariate Analysis			Multivariate Analysis			Univariate Analysis			Multivariate Analysis		
	HR	95 CI%	P	HR	95 CI%	P	HR	95 CI%	P	HR	95 CI%	P
Age in years (>50 vs ≤50)	0.655	0.283–1.519	0.324				0.844	0.470–1.515	0.570			
Gender (Female vs Male)	0.045	0.000–173.11	0.462				1.303	0.466–3.648	0.614			
ECOG PS (1 vs 0)	0.413	0.150–1.135	0.086				**0.419**	**0.202–0.872**	**0.020**	**0.350**	**0.151–0.808**	**0.014**
AFP (>400 vs ≤400 ng/mL)	1.280	0.584–2.807	0.538				1.426	0.801–2.538	0.227			
HBV (positive vs negative)	1.421	0.329–6.149	0.638				1.572	0.563–4.388	0.388			
Maximum diameter (>10 vs ≤10 cm)	0.727	0.323–1.634	0.440				0.771	0.414–1.435	0.412			
BCLC stage (A vs B and C)	1.892	0.809–4.425	0.141				1.595	0.858–2.963	0.140			
Vascular invasion (present vs absent)	1.875	0.863–4.074	0.112				1.626	0.924–2.860	0.092			
LN metastasis (present vs absent)	1.625	0.660–4.001	0.291				1.222	0.631–2.366	0.551			
Distant metastasis (present vs absent)	**3.673**	**1.581–8.536**	**0.002**	2.195	0.852–5.651	0.103	**2.119**	**1.042–4.310**	**0.038**	**3.405**	**1.600– 0.242**	**0.001**
Tumor number (multiple vs single)	**4.412**	**1.300–14.969**	**0.017**	**7.023**	**1.332–37.020**	**0.022**	**2.506**	**1.248–5.032**	**0.010**	2.147	0.985–4.681	0.055
Tumor distribution (bilobar vs unilobar)	**3.166**	**1.273–7.871**	**0.013**	1.929	0.696–5.341	0.206	**2.073**	**1.135–3.787**	**0.018**	1.331	0.675–2.626	0.410
Cirrhosis (present vs absent)	1.508	0.654–3.477	0.336				1.067	0.543–2.098	0.851			
Cycles of HAIC (>4 vs ≤4)	0.653	0.288–1.482	0.308				0.608	0.324–1.142	0.122			
Chemotherapeutic dose (reduced vs full)	1.530	0.707–3.311	0.280				1.046	0.598–1.830	0.875			
5-FU infusion time in hour (46 vs 23)	0.627	0.252–1.562	0.316				0.717	0.372–1.382	0.320			
DEB-TACE times (≥2 vs.1)	**0.266**	**0.079–0.900**	**0.033**	0.325	0.075–1.410	0.133	0.675	0.367–1.244	0.208			
ALT (>40 vs ≤40 U/mL)	1.067	0.484–2.351	0.873				**2.076**	**1.049–4.108**	**0.036**	**2.390**	**1.176–4.858**	**0.016**
ALB (>40 vs ≤40 g/L)	0.567	0.266–1.212	0.143				0.882	0.504–1.545	0.661			
TBIL (>20.5 vs ≤20.5 μmol/L)	1.122	0.444–2.839	0.808				0.829	0.438–1.568	0.564			
CRE (>75 vs ≤75 μmol/L)	1.756	0.778–3.964	0.175				0.785	0.436–1.412	0.419			
HAIC response (yes vs no, RECIST)	0.948	0.432–2.078	0.894				1.074	0.603–1.911	0.808			
HAIC response (yes vs no, mRECIST)	0.988	0.365–2.677	0.981				1.101	0.572–2.122	0.773			
DEB-TACE response (yes vs no, RECIST)	0.467	0.062–3.524	0.460				0.625	0.244–1.599	0.327			
DEB-TACE response (yes vs no, mRECIST)	**0.347**	**0.136–0.887**	**0.027**	**0.348**	**0.133–0.914**	**0.032**	**0.456**	**0.240–0.864**	**0.016**	**0.386**	**0.197–0.759**	**0.006**

Note: Statistical significances are marked in bold.

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AFP, alpha-fetoprotein; HBV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; LN, lymph node; HAIC, hepatic artery infusion chemotherapy; DEB-TACE, drug-eluting bead transarterial chemoembolization; ALT, alanine transaminase; ALB, albumin; TBIL, total bilirubin; CRE, creatinine; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST.

Table 4 Summary of Adverse Events by Severity

Adverse event	Entire Procedure		HAIC-Related	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Total	76 (100.0%)	14 (18.4%)	73 (96.1%)	7 (9.2%)
Hypoalbuminemia	59 (77.6%)	1 (1.3%)	39 (51.3%)	1 (1.3%)
Anemia	50 (65.8%)	1 (1.3%)	34 (44.7%)	0
Abdominal pain	42 (55.3%)	0	29 (38.2%)	0
ALT level elevated	34 (44.7%)	1 (1.3%)	26 (34.2%)	0
Leukopenia	28 (36.8%)	2 (2.6%)	20 (26.3%)	2 (2.6%)
Neutropenia	24 (31.6%)	3 (3.9%)	20 (26.3%)	3 (3.9%)
Thrombocytopenia	20 (26.3%)	4 (5.3%)	14 (18.4%)	4 (5.3%)
Dysuria	13 (17.1%)	0	13 (17.1%)	0
Poor appetite	14 (18.4%)	0	12 (15.8%)	0
Fever	18 (23.7%)	0	10 (13.2%)	0
Nausea	11 (14.5%)	0	9 (11.8%)	0
Hyperbilirubinemia	25 (32.9%)	2 (2.6%)	7 (9.2%)	0
Diarrhea	7 (9.2%)	0	7 (9.2%)	0
PT prolonged	10 (13.2%)	0	6 (7.9%)	0
Cough	9 (11.8%)	0	5 (6.6%)	0
Rash	7 (9.2%)	0	5 (6.6%)	0
Constipation	6 (7.9%)	0	5 (6.6%)	0
Vomiting	5 (6.6%)	0	4 (5.3%)	0
Hiccups	5 (6.6%)	0	4 (5.3%)	0
Bloating	5 (6.6%)	0	4 (5.3%)	0
Insomnia	4 (5.3%)	0	3 (3.9%)	0
Pneumonia	2 (2.6%)	1 (1.3%)	2 (2.6%)	1 (1.3%)
Hypertension	4 (5.3%)	1 (1.3%)	2 (2.6%)	0
Hypothyroidism	2 (2.6%)	0	2 (2.6%)	0
CRE level elevated	3 (3.9%)	0	1 (1.3%)	0
AUGIB	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
Hepatic encephalopathy	1 (1.3%)	1 (1.3%)	1 (1.3%)	1 (1.3%)
Cholecystitis	1 (1.3%)	0	1 (1.3%)	0
Cholangitis	1 (1.3%)	0	1 (1.3%)	0
Phlebitis	1 (1.3%)	0	1 (1.3%)	0
Allergy	1 (1.3%)	0	1 (1.3%)	0

Abbreviations: HAIC, hepatic artery infusion chemotherapy; ALT, alanine transaminase; PT, prothrombin time; CRE, creatinine; AUGIB, acute upper gastrointestinal bleeding.

hypoalbuminemia (77.6%), anemia (65.8%), abdominal pain (55.3%), elevated ALT level (44.7%), and leukopenia (36.8%); grade 3 or 4 AEs occurred in 14 (18.4%) patients and mostly included thrombocytopenia, neutropenia, leukopenia, and hyperbilirubinemia. The most frequent AEs after HAIC alone were hypoalbuminemia (51.3%), anemia (44.7%), abdominal pain (38.2%), elevated ALT level (34.2%), and leukopenia (23.4%); grade 3 or 4 AEs occurred in 7 (9.2%) patients and mostly included thrombocytopenia, neutropenia, and leukopenia. Overall, the most common AEs were mainly related to liver dysfunction and hematopoietic impairment, but most were mild to moderate and returned to normal after symptomatic treatment.

Discussion

Treatment of large HCC with cTACE necessitates the administration of substantial volumes of chemotherapy drugs and lipiodol, thereby increasing the risk of liver failure and other chemotherapy-related complications.[32,33] Considering the currently suboptimal outcomes of patients with large HCC who have undergone other treatment approaches,[7,8] we devised a strategy of initial HAIC followed by DEB-TACE. In our treatment design, a lower tumor burden after HAIC

facilitated complete embolization of tumor vasculature, and the use of less amount of embolic agents reduced the incidence of liver failure and embolization syndromes.

To minimize tumor burden, almost all patients received anti-VEGFR drugs and PD-1/PD-L1 inhibitors in addition to HAIC, which is one of the most effective regimens for tumor shrinkage, with a reported ORR rate of up to 60% to 80%.[15–17] HAIC, anti-VEGFR, and PD-1/PD-L1 inhibitors have a synergistic "1 + 1 + 1 > 3" effect. HAIC reduces tumor burden by maintaining high chemotherapeutic drug concentrations in the tumor. Conversely, immunogenic cell death induced by chemotherapy enhances the antitumor effects of PD-1/PD-L1 inhibitors.[34,35] Anti-VEGFR can enhance the antitumor activity of PD-1/PD-L1 inhibitors by inhibiting immunosuppressive cells, such as Tregs, and promoting immune T cell infiltration into the tumor microenvironment.[36] Moreover, the combination of anti-VEGFR and PD-1/PD-L1 inhibitors may overcome FOLFOX resistance by normalizing the tumor vasculature and disrupting the hypoxic tumor microenvironment.[37] Therefore, triple therapy with anti-VEGFR, PD-1/PD-L1 inhibitors, and HAIC can exert a relatively strong tumor-shrinking effect and rapidly reduce tumor burden.

The main difficulty of our strategy was determining the timing of DEB-TACE. The aim of our strategy was to first minimize tumor burden using HAIC to facilitate complete embolization of the residual tumor, then alleviate embolization-related AEs by reducing the amount of embolic agents. Therefore, in our practice, DEB-TACE was considered when our criteria for significant tumor regression were met. Our previous studies demonstrated that significant tumor response occurred until after 2–6 cycles of HAIC, which directly kills tumor cells and activates antitumor immunity by inducing immunogenic death and synergistically potentiating PD-1/PD-L1 inhibitors.[12,35,38] Therefore, in this study, HAIC was continued after 2–4 cycles if there was no significant tumor response. In a few cases that did not show significant tumor response after 5–6 cycles of HAIC, we decided to proceed to DEB-TACE, because we considered that the tumor may not be sensitive to chemotherapeutic agents and HAIC was not beneficial.

Two studies have reported on the strategy of FOLFOX-HAIC in combination with c-TACE[39] or blank embolization (TAE)[40] for the treatment of intermediate or advanced stage HCC. The median PFS in these studies was 7.9 and 8.0 months, respectively. A better PFS (11.7 months) appeared to be obtained in our study compared to c-TACE+HAIC or TAE+HAIC, despite the greater tumor burden in our study, which may be attributed to the superior anticancer activity of DEB-TACE compared to c-TACE or TAE.[41] In addition, DEB-TACE led to a substantially lower level of chemotherapeutics in the systemic circulation compared with c-TACE.[19] Thus, DEB-TACE may be a more appropriate treatment for large or huge HCC.

Given the unique strategy of our protocol, no previous clinical studies are available for direct comparison. We searched for published studies that involved patients with similar HCC tumor burden and received similar combination therapies. Huang et al[24] conducted a study on FOLFOX-HAIC plus simultaneous DEB-TACE for large unresectable HCC. Their protocol involved major chemoembolization of the tumor with DEB-TACE and reserving the microcatheter at the feeding artery for HAIC. They reported a favorable ORR of 71%, but this was lower than the ORR of 94.2% in our study. Moreover, the median OS in our study was 28.1 months, which was substantially longer than the 19.0 months that they reported. Notably, their study reported a higher rate of grade 3–4 AEs (37.7%), compared with the 18.4% rate in this study. In particular, the incidence of grade 3–4 AEs associated with liver dysfunction was higher in their study than in this study (23.2% vs 5.2%), probably because of their simultaneous use of a substantial amount of embolic and chemotherapy agents and the higher distribution of the chemotherapeutic agents in the normal liver after embolization of the dominant tumor-feeding vessels. On the contrary, our protocol first administered HAIC to minimize tumor burden, after which the residual tumor was eliminated by minor embolization to avoid synthetic toxicity.

This study had some limitations. First, the single-arm and single-center design may have constrained the sample size. Therefore, generalizing the results to other settings should be done with caution. Moreover, the efficacy and safety of this treatment protocol in clinical practice require further verification by prospective multicenter studies with larger sample size. Second, there was no standard threshold on the number of HAIC cycles before DEB-TACE. In practice, the timing of DEB-TACE was determined by the surgeon based on the results of enhanced CT/MR or DSA imaging; therefore, implementation of this strategy was largely subjective and may pose difficulties in generalizability. Our subgroup analysis did not identify the optimal number of HAIC cycles with sequential DEB-TACE for the best efficacy; this remains to be answered by further analysis of a larger population.

Conclusions

In this single-center, retrospective study, our results suggested that FOLFOX-HAIC with sequential DEB-TACE demonstrated promising efficacy and safety for patients with unresectable HCC with a maximum tumor diameter of ≥7 cm. This combination strategy provided a new potential first-line treatment option for these patients, although validation by a multicenter, randomized, controlled Phase 3 clinical trial is required.

Data Sharing Statement

All data used during the study are available from the corresponding author Rongping Guo upon reasonable request.

Ethics Statement

This study was conducted according to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee (B2020-318-01) of Sun Yat-Sen University Cancer Center (SYSUCC; Guangzhou, China).

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Author Contributions

All authors R.Z., J.Z., Z.Z., X.X., Q.W., S.L., W.W., and R.G. made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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