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ORIGINAL ARTICLE

Combination of TACE and FOLFOX4 in the treatment of unresectable advanced hepatocellular carcinoma: a prospective cohort study*

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Abstract

Objective The aim of the study was to assess the effectiveness and safety of a combined therapy with transcatheter arterial chemoembolization (TACE) and FOLFOX4, in patients with unresectable advanced hepatocellular carcinoma (HCC).

Methods In this study, patients with advanced HCC, that received treatment between November 2015 and October 2017, were recruited. Among these, 30 patients were treated with TACE only (TACE group); whereas 33 patients were treated with a combination of FOLFOX4 chemotherapy and TACE (combination group). Survival analyses, including overall survival (OS) and progression free survival (PFS) analysis, were performed for both groups. Following this, the responses of patients to treatment were evaluated every 3 months, and the toxic and adverse events were observed.

Results The median follow-up time was 9.2 months (3–36 months). In the combination group, at 3 months, a disease control rate (DCR) of 60.6%, and a median OS of 9.1 months was obtained [95% confidence interval (CI) 6.5–11.7]. In the TACE group, the DCR and OS were 33.3% and 5.5 months (95% CI 4.3–6.7), respectively. On the other hand, the PFS in the combination and TACE groups were observed as 5.6 months (95% CI 3.6–7.6) and 2.6 months (95% CI 2.0–3.2), respectively. Both these findings indicate a statistically significant difference (P = 0.01) between both the groups. Similar TACE associated adverse events were observed in both groups. In the combination group, frequently observed FOLFOX4 related adverse effects included nausea (90.9%), leukopenia (75.8%), thrombocytopenia (69.7%), and vomiting (69.7%). Most adverse reactions were between grades I–III and were alleviated after symptomatic treatments.

Conclusion The combination of TACE with FOLFOX4 therapy has better effectivity and safety than TACE alone.

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Key words: advanced hepatocellular carcinoma; transcatheter arterial chemoembolization (TACE); FOLFOX4

Hepatocellular carcinoma (HCC) represents a serious threat to public health and is a medical burden worldwide. This is especially true for China, with its high rate of hepatitis B and C infection [1–2]. Globally, HCC is one of the five most common types of cancer. In addition, approximately 50% of all new cases are diagnosed in China [3]. The diagnosis of HCC is often difficult, due to its insidious onset and atypical early symptoms. Most patients reach an advanced stage or have distant metastases by the time HCC is identified. As a result, less than 20% of the diagnosed cases are eligible for surgical treatment [4]. Currently, transcatheter arterial chemoembolization (TACE) is one of the most commonly used methods for the treatment of advanced HCC. TACE has been proven to delay tumor progression and vascular invasion. It can also prolong patient survival through several years of clinical application [5–6]. Moreover, TACE can selectively destroy HCC tissues and is believed to be a suitable option for patients with cirrhosis [7]. Molecular targeted drugs, such as sorafenib or regorafenib, are still the only choice for drug treatment of patients that are not surgical candidates. However, the efficiency of

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these agents is far from satisfactory. In addition, there are significant obstacles to the widespread use of these agents [8–10]. First, patients with advanced HCC often have compromised gastrointestinal function, that influences the absorption of orally administered drugs [11]. Second, the daily dose of sorafenib is very high (over 800 mg, p.o.) and it produces serious side effects during clinical usage. In addition, this agent is expensive, and its usage places a heavy financial burden on the patient or their family. Third, only a small proportion of patients are observed to have neoplasms that are initially sensitive to sorafenib. In some cases, the tumor developed a resistance to sorafenib during treatment [12]. Some of the newly approved molecular targeted agents, such as regorafenib or lenvatinib, are used clinically for only a short period of time. The deficiencies of these agents, including high cost, rapid onset of drug-resistance, and high toxicity are gradually becoming apparent following their widespread applications. Therefore, developing novel and effective anti-tumor drugs or strategies will not only help achieve improved clinical outcomes, but will also provide patients with better treatment choices.

The role of traditional chemotherapy in advanced HCC may be controversial. However, traditional chemotherapies offer more choices at a lower cost than the molecularly targeted drugs [13]. Therefore, a breakthrough involving the use of chemotherapies for advanced HCC may be of great significance. Qin *et al* evaluated the effectivity and safety of FOLFOX4 chemotherapy in the treatment of advanced HCC, over a single drug therapy with doxorubicin [14]. This study revealed that FOLFOX4 treatment significantly improved the objective response rate (ORR) and disease control rate (DCR) in Chinese patients with HCC and significantly prolonged their survival [14]. Based on this breakthrough, the "Guidelines for the diagnosis and treatment of primary liver cancer (2017)", recommended that FOLFOX4 chemotherapy be made available as a therapy for advanced HCC [15]. Moreover, the use of combination treatments with agents that employed various mechanisms, was viewed as the future of anti-tumor therapy [16–18]. As a targeted therapy, the use of TACE can induce tumor necrosis and reduce the tumor burden. It is observed that approximately 30%–50% of patients develop extensive tumor necrosis after TACE treatment [19]. Similarly, FOLFOX4 chemotherapy is a systemic treatment that can delay tumor progression via synergistic anti-proliferative activity [20]. Thus, hepatic arterial chemoembolization combined with FOLFOX4 chemotherapy may achieve better therapeutic effects against advanced HCC than the use of TACE alone. Studies assessing the effect of TACE combined with FOLFOX4 in the treatment of advanced HCC are limited. Therefore, the present study was designed to prospectively analyze the effectiveness and safety of TACE combined with FOLFOX4 chemotherapy in patients with advanced liver cancer.

Materials and methods

General information

This prospective cohort study enrolled 63 consecutive patients, that were diagnosed with unresectable advanced hepatocellular carcinoma, and received treatment between November 2015 to October 2017, at our hospital (The Fifth Medical Center of PLA General Hospital, Beijing, China). The diagnoses were performed via histology or via dynamic enhancement magnetic resonance imaging (MRI)/computed tomography (CT), in accordance with the Barcelona Clinic Liver Cancer Staging (BCLC) Classification [21]. As per their wishes, the patients received either TACE alone (TACE group, n = 30), or TACE plus FOLFOX4 regimen (combination group, n = 33). All patients enrolled refused to be treated with molecular targeted drugs. The study protocol was approved by the Ethics Committee of our center (The Fifth Medical Center of PLA General Hospital, Beijing, China). The protocol number is 2014185D. All patients signed a written-informed consent prior to their enrollment in the study.

Inclusion criteria

The inclusion criteria were as follows: (1) age 18 to 75 years; (2) Karnofsky performance status (KPS) score ≥ 70; (3) dynamic enhanced MRI/CT or pathological diagnosis as advanced HCC (BCLC C Stage); (4) having lesions that could be evaluated objectively but could not be treated surgically; (5) Child-Pugh scores ≤ 7; (6) expected survival times > 3 months; (7) neutrophil counts ≥ 1.5×10^9 /L and platelet counts ≥ 75×10^9 /L.

Exclusion criteria

The exclusion criteria were as follows: (1) presence of other systemic diseases, such as coronary heart disease, cerebrovascular accidents, and mental and neurologic diseases; (2) liver dysfunction (Child-Pugh C grade), with coagulation disorders that were untreatable, combined with untreatable active infections; (3) pregnancy or active menstruation for women; (4) allergy to chemotherapeutic drugs included in the FOLFOX4 regimen; (5) presence of tumors in other tissues; (6) dyscrasias or multiple organ failure; (7) parallel use of other drugs such as chemotherapeutic drugs or treatment with traditional Chinese medicine.

Treatment protocols

All patients were routinely treated with TACE. Once the liver functions recovered 3–5 days after completion of the TACE treatment, the FOLFOX4 regimen was

administered.

For TACE, routine preoperative preparation was performed. The Seldingers method was employed to catheterize the femoral artery, and to allow the arteriography of the hepatic and superior mesenteric arteries. This was followed by an assessment of tumor staining, and the filling of the portal veins. The vessel supplying the tumor was selectively catheterized, followed by the slow injection of fluorouracil 0.5–1.0 g, epirubicin 20–40 mg, and lipiodol emulsion embolization of 5–25 mL into the target vessel. The patients with extrahepatic metastasis were treated with chemoembolization. The amount of iodized oil was determined according to tumor size. Finally, the artery supplying the tumor was embolized using Gelfoam particles. TACE was performed according to the tumor response and patients' health status and was usually repeated no more than four times per six months.

FOLFOX4 chemotherapy was performed with oxaliplatin 85 mg/m^2 (intravenous infusion for 2 h on the first day), leucovorin 200 mg/m^2 (intravenous infusion for 2 h on the first and second days), and fluorouracil (400 mg/m^2, intravenous injection; 600 mg/m^2, continuous intravenous infusion for 22 h on the first and second days). An interval of two weeks was defined as one cycle The treatment was continued until it was completed, or until the patient was intolerant due to toxic side effects, or died. The treatment lasted for no more than 12 cycles.

Follow-up

The duration of this study was from the day of commencement of the treatment to April 30th, 2019, or until the death of the patient. During the follow-up period, there existed no events that were considered as competing risks significantly affecting the patients mortality and prognoses.

Observation indicators and evaluation methods

Routine blood tests including liver and renal function test, tests for alpha fetal protein (AFP) levels, and abdominal enhanced MRI/CT and chest CT scans were performed before and after the treatment. The patient's condition was reviewed and evaluated every 6 weeks. Effectiveness outcomes included the median or 95% CI of overall survival (OS), progress-free survival (PFS) and 3-month tumor response, including ORR and DCR. OS was defined as the period from commencement of treatment to the end of the follow-up period or death. PFS was defined as the time interval between commencement of treatment and tumor progression or death. Tumor response was evaluated according to the modified guidelines for Response Evaluation Criteria in Solid Tumors [22], and included complete response (CR, in which arterial enhancement disappeared in all target lesions), partial response [PR, reduction of the diameter of the target lesion (shown by enhanced imaging at the arterial phase) by no less than 30%], stable disease (SD, reduction of the diameter of the target lesion not reaching PR, or the increase in the diameter of the target lesion not reaching PD), and progressive disease (PD, diameter increase of the target lesion by no less than 20% and/or the occurrence of new lesions). The ORR was defined as the percentage of CR and PR among all patients. The DCR was defined as the percentage of total cases indicating CR, PR, and SD.

According to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [23], the toxicity of chemotherapy was divided into degrees 0–4. According to the oxaliplatin specialized Levi neuropathy grading criteria [24], the toxicity of the nervous system was divided into grades 0 to 4: grade 0 indicated no response; grade 1 indicated abnormal feeling or insensitivity (caused by cold) that resolved completely within 7 days; grade 2 indicated abnormal feeling or insensitivity that resolved completely within 21 days; grade 3 indicated abnormal feeling or insensitivity with no recovery within 21 days; and grade 4 indicated abnormal feeling or insensitivity, accompanied by dysfunction.

Statistical analysis

Count data were expressed as number and percentages and were analyzed by the Chi-square test or Fisher's exact test as appropriate. Measurement data were expressed as mean and standard deviation (SD), and were analyzed by Student's *t*-tests. Survival was estimated by the Kaplan-Meier method. The log-rank test was used to compare the survival rates between the two groups. Software from the SPSS 23.0 statistical package (IBM Corp, Armonk, NY, USA) was employed for data analysis.

Results

Baseline characteristics of patients

As represented in Table 1, 33 and 30 cases of unresectable advanced HCC were treated with TACE + FOLFOX4 and TACE only, respectively. There were no significant differences between patient age (P = 0.378), gender distribution (P = 0.461), tumor number (P = 0.993), vascular involvement (P = 0.288), metastases (P = 0.942), AFP and cholinesterase levels (P = 0.271 and 0.102, respectively), tumor diameter (P = 0.919), Child-Pugh classification (P = 0.646), TACE number (P = 0.288), and the various pathologies (P = 0.224). The median number of chemotherapy cycles utilized in the combination group was 5 (range, 2–13 cycles). Therefore, no significant differences in these parameters between these two groups of patients were identified.

Table 1 Baseline characteristics of patients [*n* (%)]

Parameter	TACE + FOLFOX4 (*n* = 33)	TACE (*n* = 30)	*P* value
Age (years), mean ± SD	53.94 ± 8.79	55.3 ± 12.4	0.378
Sex			0.461
Male	29 (87.9)	28 (93.3)	
Female	4 (12.1)	2 (6.7)	
Tumor number			0.993
1	8 (24.2)	7 (23.3)	
2	2 (6.1)	2 (6.7)	
≥ 3	23 (69.7)	21 (70.0)	
Vascular involvement			0.288
None	16 (48.5)	9 (30.0)	
Branch of portal vein	10 (30.3)	14 (46.7)	
Main portal vein	7 (21.2)	7 (23.3)	
Metastasis			0.963
No	14 (42.4)	13 (43.3)	
Yes	19 (57.6)	17 (56.7)	
Lung	12	10	
Lymph node	7	7	
AFP (ng/mL)			0.271
< 20	6 (18.2)	9 (30.0)	
≥ 20	27 (81.8)	21 (70.0)	
Cholinesterase (U/L)			0.102
≤ 5000	13 (39.4)	18 (60.0)	
> 5000	20 (60.6)	12 (40.0)	
Tumor diameter (cm), mean± SD	7.55 ± 3.72	7.59 ± 3.68	0.919
Child-Pugh classification			0.646
A	26 (78.8)	25 (83.3)	
B	7 (21.2)	5 (16.7)	
Number of TACE			0.288
1	7 (21.2)	2 (6.7)	
2	14 (42.4)	9 (30.0)	
≥ 3	12 (36.4)	19 (63.3)	
Pathology			0.224
Hepatitis B	25 (75.7)	29 (96.7)	
Hepatitis C	4 (12.1)	1 (3.3)	
Alcoholic liver disease	2 (6.1)	1 (3.3)	
Others	2 (6.1)	0	

Positive tumor response

In the combination group, ORR and DCR at 3 months were 39.4% (95% CI: 22.8%–56.0%) and 60.6% (95% CI: 48.1%–73.1%), respectively. In comparison, the ORR and DCR were 13.3 % (95% CI: 7.5%–19.1%) and 33.3% (95% CI: 22.8%–43.8%) in the TACE group, respectively (Table 2). These findings indicate that the ORR (P = 0.045) and DCR (P = 0.030) were significantly higher in the combination-therapy group than in the TACE group. Moreover, PD was markedly less common in the combination group as compared to that in the TACE group (P = 0.014; Table 2). And indicated in Fig. 1 and 2, combination therapy can significantly reduce the intrahepatic and intrapulmonary lesions in patients with advanced hepatocellular carcinoma and pulmonary metastasis.

Table 2 Treatment response of patients [n (%)]

	TACE + FOLFOX4 (*n* = 33)	TACE (*n* = 30)	*P* value
CR	0	0	
PR	13 (39.4)	4 (13.3)	0.045
SD	7 (21.2)	6 (20.0)	0.040
PD	13 (39.4)	20 (66.7)	0.014
ORR	13 (39.4) (95% CI: 22.8%–56.0%)	4 (13.3) (95% CI: 7.5%–19.1%)	0.045
DCR	20 (60.6) (95% CI: 48.1%–73.1%)	10 (33.3) (95% CI: 22.8%–43.8%)	0.030

Note: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate = CR + PR; DCR, disease control rate = CR + PR + SD

Table 3 TACE related adverse events [n (%)]

Adverse event	TACE + FOLFOX4 (*n* = 33)	TACE (*n* = 30)	*P* value
Fever	28 (84.8)	26 (86.7)	0.095
Nausea and vomiting	18 (54.5)	15 (50.0)	0.718
Abdominal pain	19 (57.6)	14 (46.7)	0.387
Liver function damage	27 (81.8)	26 (86.7)	0.857
Leukopenia and thrombocytopenia	1 (3.0)	1 (3.3)	1.000
Puncture point bleeding	2 (6.1)	1 (3.3)	1.000

Prolonged survival

The follow-up periods ranged from 3 to 36 months, with a median value of 9.2 months. In the combination-therapy group, 28 patients died and 5 survived. In the TACE group, 26 died and 4 survived. In the combination group, the median OS was 9.1 months (95% CI: 6.5–11.7 months), while in the TACE group the median OS was 5.5 months (95% CI: 4.3–6.7 months). This represents a significant difference in OS between the two groups (P = 0.006; Fig. 3a). Moreover, the PFS values were observed as 5.6 months (95% CI 3.6–7.6) and 2.6 months (95% CI 2.0–3.2) in the combination and TACE groups, respectively, also representing a significant difference (P = 0.01; Fig. 3b). The patients were further divided into two groups, portal vein tumor thrombus (PVTT) group and no-PVTT group. There is no statistically significant difference in OS and PFS of no-PVTT group treated with TACE or combination-therapy. However, the combination-therapy may have influenced and increased the OS and PFS of no-PVTT group (Fig. 4a–4b). As compared with TACE alone, the combination-therapy may increase the OS and PFS of patients with PVTT (Fig. 4c–4d).

Similar adverse events

TACE associated adverse events, including fever (P = 0.095), nausea and vomiting (P = 0.718), abdominal pain

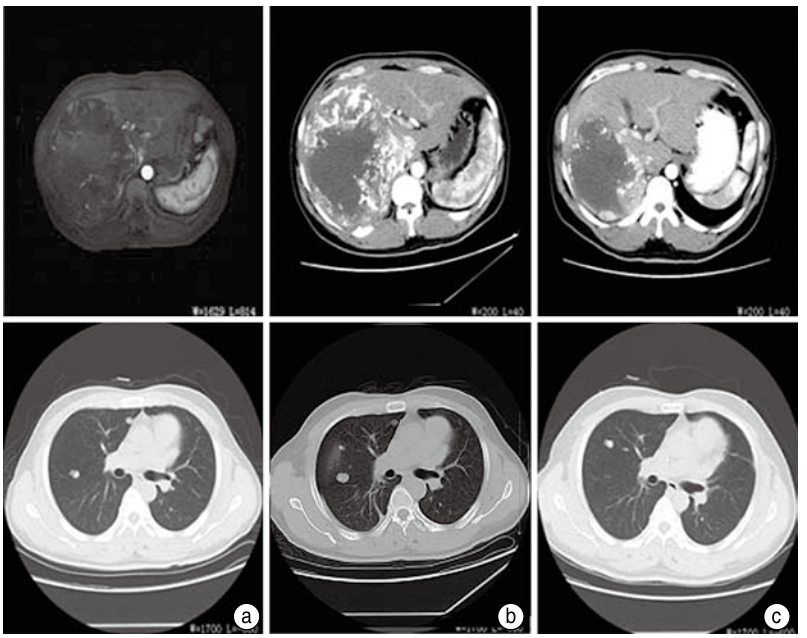

Fig. 1 Tumor response in a patient with massive hepatocellular carcinoma and double lung metastases. (a) Diagnosis of massive hepatocellular carcinoma with double lung metastases. (b) After the first TACE, lipiodol accumulation at the site of liver cancer, enlarged intrahepatic tumor, and a significant increase in double lung metastases compared with (a); following which the patient received systemic chemotherapy. (c) The patient received systemic chemotherapy for four times after the second TACE, intrahepatic tumor reduced (17 cm to 10 cm) and double lung metastases declined

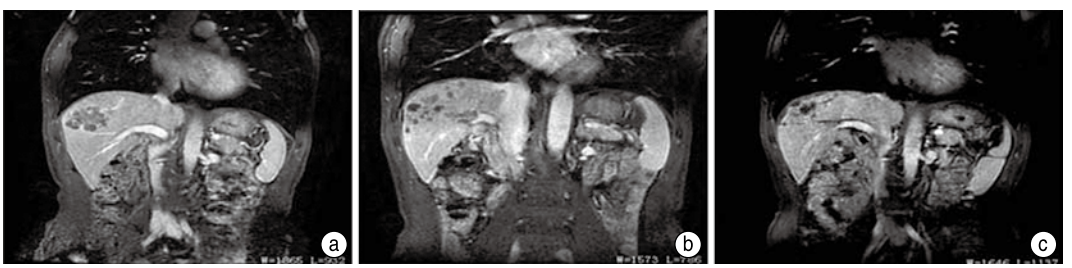

Fig. 2 Tumor response in a patient with PVTT. (a) Before the first TACE, imaging indicated a tumor in liver right lobe, with incomplete capsule and no obvious PVTT (AFP was 13 ng/mL). (b) After the third TACE, intrahepatic tumor was enlarged and was accompanied with tumor thrombus in the right branch of the portal vein (AFP, 159 ng/mL); following this, the patient received systemic chemotherapy and a fourth TACE. (c) The patient then received systemic chemotherapy for three cycles after the fourth TACE; tumor and tumor thrombus were reduced (AFP, 71 ng/mL).

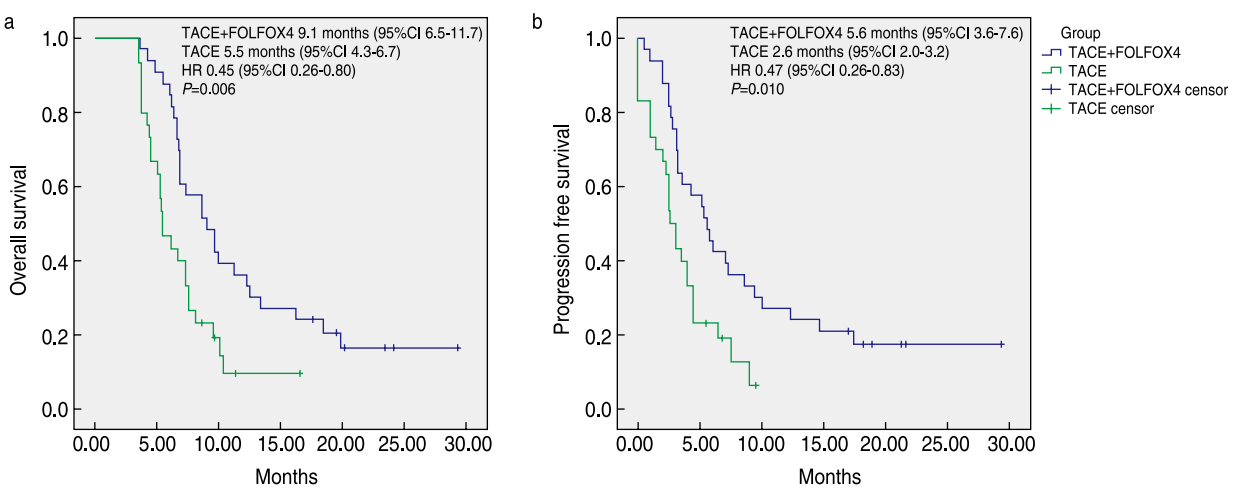

Fig. 3 OS and PFS of patients in both groups. (a) Overall survival, (b) Progression free survival

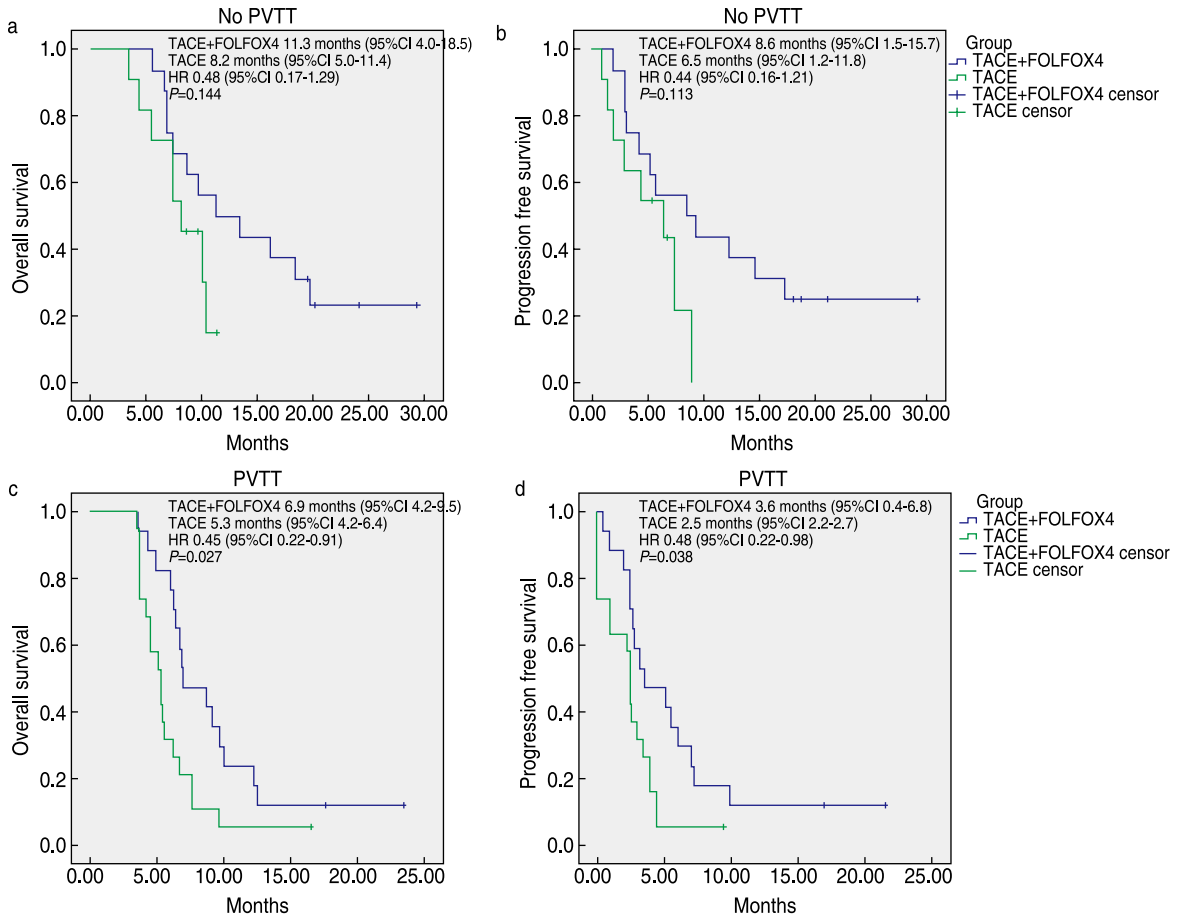

Fig. 4 OS and PFS of patients with or without PVTT. (a and c) OS; (b and d) PFS

(P = 0.387), liver function changes (P = 0.857), leukopenia and thrombocytopenia (P = 1.000), and puncture site bleeding (P = 1.000), were similar in both groups (Table 3). In the combination group, the adverse events frequently observed after treatment with FOLFOX4 included nausea (90.9%), leukopenia (75.8%), thrombocytopenia (69.7%), and vomiting (69.7%). Allergies (3%) and peripheral neuropathy (15.2%) were observed in some cases. However, the adverse events mostly ranged between grades I–III, and alleviated after symptomatic treatments (Table 4).

Discussion

This study compared the safety and effectiveness of TACE and a combination of TACE and FOLFOX4

Table 4 FOLFOX4 related adverse events [*n* (%)]

Adverse event	TACE + FOLFOX4 (*n* = 33)					
	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3–4
Leukopenia	25 (75.8)	9 (27.3)	10 (30.3)	4 (12.1)	2 (6.1)	6 (18.2)
Thrombocytopenia	23 (69.7)	7 (21.2)	11 (33.3)	5 (15.2)	0	5 (15.2)
Nausea	30 (90.9)	20 (60.6)	7 (21.2)	2 (6.1)	1 (3.0)	3 (9.1)
Vomiting	23 (69.7)	15 (45.5)	7 (21.2)	1 (3.0)	0	1 (3.0)
Bilirubin elevation	8 (24.2)	4 (12.1)	3 (9.1)	1 (3.0)	0	1 (3.0)
Transaminase elevation	9 (27.3)	8 (24.3)	1 (3.0)	0	0	0
Allergy	1 (3.0)	1 (3.0)	0	0	0	0
Peripheral nerve toxicity	5 (15.2)	5 (15.2)	0	0	0	0
Pigmentation	14 (42.4)	14 (42.4)	0	0	0	0

regimen, in the treatment of HCC patients with unresectable lesions. We observed that the combination of the FOLFOX4 regimen with TACE resulted in improved clinical outcomes including increased OS, PFS, ORR, and DCR, and reduced PD.

TACE is an effective local treatment for advanced HCC. As compared to controls, it leads to a significantly improved 1-year survival rate [25]. There have been studies comparing the combination therapy of TACE and molecularly targeted drugs, including sorafenib, and therapy with TACE alone. From these studies it was indicated that the combination group experienced improved overall 1-year survival and disease control rate [26]. However, studies combining TACE and chemotherapy, for example FOLFOX4, have not been performed in the past. In the present study, an OS of 9.1 months (95%CI 6.5–11.7) and 5.5 months (95% CI 4.3–6.7) were obtained for the combination group and TACE group, respectively These findings indicate that combining the FOLFOX4 regimen with TACE is superior to TACE alone. Other treatment outcomes followed a similar trend.

In addition, we carried out a subgroup analysis based on PVTT. The results indicate that patient survival outcomes (OS and PFS) were more favorable in the no-PVTT subgroups as compared with those in the PVTT groups (Fig. 4). However, our findings also demonstrate that, PVTT patients treated with the FOLFOX4 + TACE combination showed a higher survival than those treated with TACE alone. The same is true for patients with extrahepatic metastasis. Two cases that were treated by this combination are represented in Figs. 1 and 2. We found that 81.3% (13/16) of the patients with PVTT died from upper gastrointestinal hemorrhaging. This indicates that portal hypertension followed by cirrhosis and PVTT may be the major cause of death in patients with advanced HCC. We believe that with the application of portal vein stenting and radiotherapy, the goal of reducing portal vein thromboses and decreasing portal pressure can be achieved [27–29]. Moreover, incorporating FOLFOX4 chemotherapy would better control of tumor progression. Previously, we combined TACE with sorafenib treatment in 51 patients with advanced HCC, and observed that the median OS rates for the PVTT and non-PVTT groups were 6 months and 10.3 months [30], respectively. These findings indicate that the efficacy of TACE combined with FOLFOX4 chemotherapy (OS of 6.9 months and 11.3 months for the PVTT and no-PVTT, respectively) was similar to that of TACE combined with sorafenib treatment in patients with advanced hepatocellular carcinoma. It also had the advantages of lower cost and fewer side effects.

For TACE combined with FOLFOX4 in the treatment of advanced HCC, the main toxicities were gastrointestinal reactions (nausea, anorexia, and vomiting) and myelosuppression (leukopenia and thrombocytopenia). The rare side effects of this treatment included liver damage, drug allergies, and mild peripheral neurotoxicity. Grade 3–4 adverse effects were not commonly observed. Compared with the EACH study [14], it was observed that nausea, vomiting, leukocytopenia, and thrombocytopenia all increased in the combination group. This was because FOLFOX4 chemotherapy was administered for more cycles in this study (5 versus 4 times). Gastrointestinal symptoms such as nausea and vomiting could be alleviated after FOLFOX4 chemotherapy. In addition, myelosuppression was significantly relieved by treatment with granulocyte colony-stimulating factor and interleukin-11 [31–32]. Both, this study and the EACH study indicated that FOLFOX4 chemotherapy had little effect on liver function tests. It was observed that ALT increased by 27.3% and 21.86% in this and the latter studies, respectively. Additionally, the bilirubin increase rates were 24.2% and 20.22%, respectively. The main adverse effects following sorafenib treatment include hand and foot skin reactions, diarrhea, fatigue, hypertension, and liver function damage. Serious side effects often led to drug dose reductions or withdrawal. Following the development of sorafenib intolerance, up to 44% of dose reduction or drug withdrawal was required [33–34]. Of the 33 patients that were administered with FOLFOX4 and TACE, only 3 (9.1%) withdrew as a result of FOLFOX4 side effects. Two of them continued chemotherapy after symptomatic treatment. Only one patient was unable to continue treatment due to overt nausea. Interestingly, previous reports have suggested that in advanced HCC, the hepatic arterial infusion of FOLFOX4 therapy better ameliorates survival with acceptable toxicity and elevated quality of life [35–36], as compared to treatment with sorafenib. As a result, FOLFOX4 therapy could be a novel treatment for advanced HCC. Moreover, all patients in this study had presented with HCC of BCLC stage C. This is similar to the patients in the Oriental experiment (BCLC stage C: 143/150 of sorafenib group; 73/76 of placebo group). A few patients included in the SHARP experiments also presented with BCLC stage B HCC (54/299 in sorafenib group or 51/303 in placebo group).

This study has certain limitations. It was carried out in a single center with a small sample size. Therefore, larger multicenter, randomized control trials are needed to confirm these findings.

In summary, TACE combined with FOLFOX4 therapy has good efficacy, in that it prolongs the survival and improves the quality of life, with limited toxicity and adverse events. Moreover, most patients were able to tolerate this treatment. This suggests that it may be able to significantly improve the clinical approach to HCC.

Ethics approval and consent to participate

Patient data were used after obtaining approval from the Ethics Committee of the Fifth Medical Center of PLA General Hospital, Beijing, China. All research was performed in compliance with the Helsinki Declaration, with the informed written consent of patients.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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