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SHORT REPORT

Efficacy And Safety Of Raltitrexed Plus Oxaliplatin-Based Transarterial Chemoembolization In Patients With Unresectable Hepatocellular Carcinoma

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Objective: To evaluate the efficacy and safety of raltitrexed plus oxaliplatin-based transarterial chemoembolization (TACE) in patients with unresectable hepatocellular carcinoma (HCC).

Methods: A total of 123 patients with unresectable HCC were recruited into the prospective cohort study. Raltitrexed plus oxaliplatin-based TACE was performed according to the traditional method at monthly intervals and was repeated for up to 4 cycles if no disease progression or intolerable toxicity occurred. The primary efficacy endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS) and tumor response rate. The Cox proportional-hazards regression model was used to assess the independent prognostic factors of OS. Adverse events were also observed.

Results: The median OS time and PFS were 623 days (95% CI: 461, 785) and 338 days (95% CI: 302, 704), respectively. The disease control rate was 95.5% (118/123). The Cox proportional-hazards regression model indicated that age, ECOG performance status and response to TACE as independent prognostic factors of OS. No treatment-related mortality occurred within 30 days of treatment procedure. The most common complications included postembolization syndrome, liver dysfunction and hematological toxicity. Grade 3 pain, transglutaminase abnormality and thrombocytopenia were observed in 16 (13%), 15 (12.2%) and 3 (2.4%) patients, respectively. No grade 4 adverse events were observed.

Conclusion: Raltitrexed plus oxaliplatin-based TACE led to high tumor response rate and promising PFS and OS, and was considered safe and tolerable in patients with unresectable HCC.

Keywords: raltitrexed, oxaliplatin, hepatocellular carcinoma, transarterial chemoembolization

Introduction

Transarterial chemoembolization (TACE) is most commonly recommended as the first-line treatment for unresectable hepatocellular carcinoma (HCC)[1,2] and also as the standard treatment for intermediate-stage HCC.[3] However, no uniform standard protocol for TACE has been adopted globally.[2] The choice of embolizing agents used was differed by different centers, and also the schedule and interval of retreatment, especially the choice of anticancer chemotherapeutic agents used. Several chemotherapeutic agents, including doxorubicin, cisplatin, fluorouracil and mitomycin, have been used along with TACE either as a sole agent or as a combination drug regimen.[4] There is no high-quality evidence for choosing the best

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chemotherapeutic agent currently. It is imperative to explore the efficacy and safety of a new agent or regimen for treating HCC.

According to a randomized, multicenter, open-label study conducted in 2013, FOLFOX4 (infusion 5-fluorouracil, leucovorin and oxaliplatin) chemotherapy demonstrated better progression-free survival (PFS) and response rates when compared with doxorubicin alone in patients with advanced HCC.[5] Many studies have shown that intra-arterial perfusion provides higher response rates than conventional systemic chemotherapy,[6–8] and it is natural to the hypothesis that transarterial infusion of FOLFOX4 might be more effective than systemic chemotherapy. However, transarterial infusion of FOLFOX4 might be problematic as 5-fluorouracil, a component of FOLFOX4, is a time-dependent antitumor agent and requires prolonged infusion for approximately 44–48 hrs.[6] This increases the risk of catheter thrombosis and limits the mobility of patients when the catheter is inserted from the common femoral artery.

Raltitrexed is another thymidylate synthase inhibitor that is administered as a short-term infusion or mixed with lipiodol, and so it is regarded as a better candidate for TACE when compared with 5-fluorouracil. Many studies have shown that raltitrexed-based chemotherapy regimen has similar efficacy to that of FOLFOX4 in patients with advanced colorectal cancer,[9,10] and revealed a safe and effective hepatic arterial infusion of raltitrexed and oxaliplatin in patients with colorectal cancer.[6,10–13] However, the clinical data of raltitrexed in TACE for HCC are rare when compared with the data of hepatic arterial infusion of raltitrexed for advanced colorectal cancer. Hence, in the present study, the efficacy and safety of raltitrexed plus oxaliplatin-based TACE was evaluated in patients with unresectable HCC.

Patients And Methods

Selection Of Patients

This multicenter, prospective cohort study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Ethics Committee of Shandong Medical Imaging Research Institute and obtained approval from the ethics committee of Shandong Cancer Hospital and Institute, Qilu Hospital of Shandong University, Affiliated Hospital of Qingdao University, Qingdao Central Hospital, 960 Hospital of People's Liberation Army, Qianfoshan Hospital of Shandong Province and People's Hospital of Jining City. All patients provided written informed consent form. Patients were recruited from 8 centers of Shandong Province in China. The inclusion criteria were as follows: (1) patients aged >18 years with HCC who are unsuitable for resection or percutaneous ablation; (2) Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2; (3) preserved liver function (Child-Pugh Class A or B); (4) a life expectancy of more than 12 weeks and (5) a leukocyte count of $>4.0\times10^9$/L, platelet count $\geq80\times10^9$/L, hemoglobin (Hb) ≥80g/L; creatinine(Cr) ≤2.0×UNL (upper normal limits), bilirubin (BIL) ≤2.0×UNL, alanine transaminase (ALT) and aspartate transaminase (AST) ≤5.0×UNL. All patients were excluded if they had any other primary tumors, severe infection, known central nervous system metastases, and other serious illnesses or medical conditions.

Table 1 Baseline Characteristics Of The Study Population

Age	58(38–77)	N (%)
Age	<60 ≥60	82 (66.7%) 41 (33.3%)
Gender	Male Female	100 (81.3%) 23 (18.7%)
ECOG	0 1 2	63 (51.2%) 50 (40.1%) 10 (8.1%)
Etiology	Hepatitis B virus Hepatitis C virus Cirrhosis	87 (70.7%) 2 (1.6%) 12 (9.8%)
Location of tumor	Right lobe Left lobe Bilobar	77 (62.6%) 27 (22.0%) 19 (15.4%)
Number of tumors	1–3 >3	99 (80.4%) 24 (19.5%)
Lengths of the tumors	≤10cm >10cm	89 (72.4%) 34 (27.6%)
Distant metastasis	Yes No	69 (56.1%) 54 (43.9%)
AFP	≤200 ng/mL >200 ng/mL	69 (56.1%) 54 (43.9%)
Child-Pugh Score	A B	84 (68.3%) 39 (31.7%)

Treatment Plan

TACE was performed according to the traditional method. The Seldinger technique was used to obtain access to the femoral artery. Arteriography of the hepatic artery was performed to localize the tumor and obtain information regarding the feeding arteries. The tumor-feeding artery was

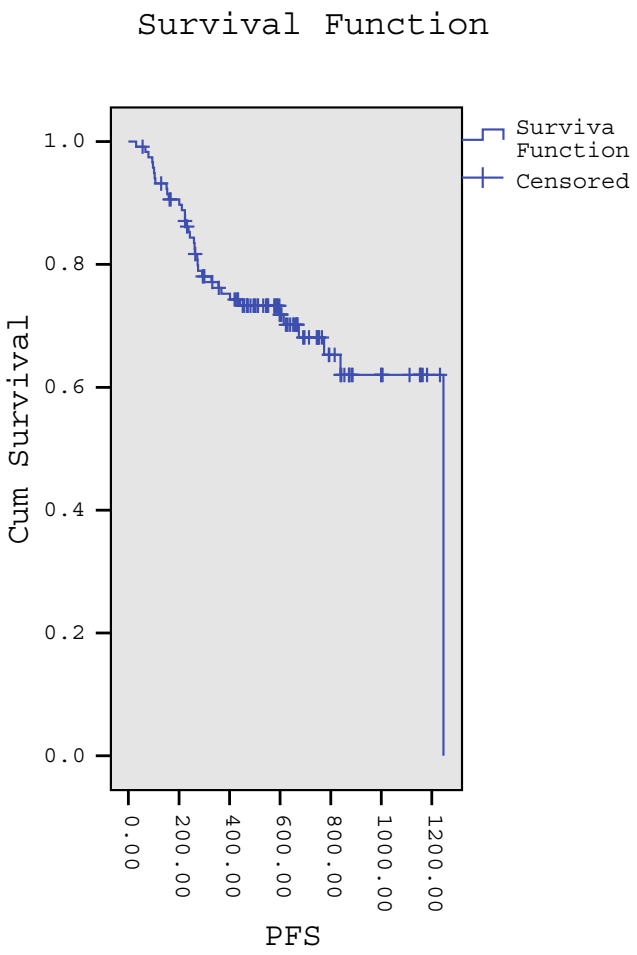

Figure 1 Kaplan – Meier curve showing the median progression-free survival in patients with unresectable hepatocellular carcinoma treated using raltitrexed plus oxaliplatin-based TACE.

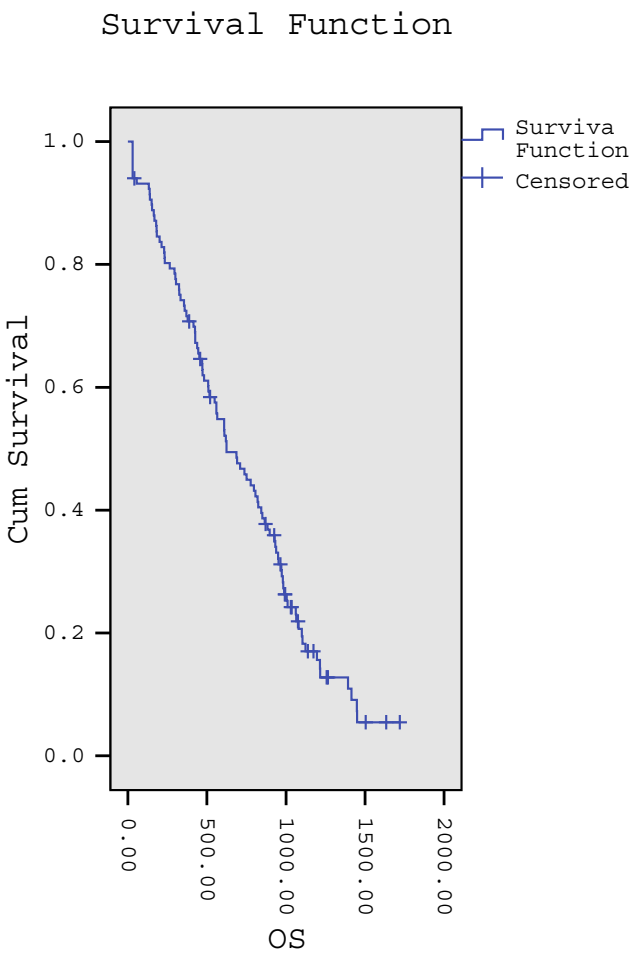

Figure 2 Kaplan – Meier curve showing the median overall survival in patients with unresectable hepatocellular carcinoma treated using raltitrexed plus oxaliplatin-based TACE.

selected or super-selected prior to chemoembolization. Oxaliplatin (100–200 mg) was infused into the feeding artery of the tumor, followed by infusion of 5–20 mL of lipiodol mixed with raltitrexed (2–4 mg) into the feeding artery until stasis flow in tumor vascularity was achieved. Gelatin sponge particles were used after embolization with lipiodol emulsion, but the use of gelatin sponge was not obliged and determined by the interventional radiologist. TACE was performed at monthly intervals and repeated for up to 4 cycles if no disease progression or intolerable toxicity occurred.

Outcomes Assessment

Efficacy

The primary efficacy endpoint was overall survival (OS), and the secondary endpoints were PFS and tumor response rate. Tumor responses were assessed using the modified response evaluation criteria in solid tumors (mRECIST). Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and laboratory analyses including complete blood cell count, blood chemistry and tumor marker level were carried out within 7 days of initiating TACE. Repeated CT/MRI and laboratory analyses were performed after 4 weeks of every TACE cycle. TACE was repeated for up to 4 cycles if no complete responses or disease progression occurred. After 4 cycles of TACE, patients were subjected to follow-up every 12 weeks for assessing PFS or OS until disease progression or death.

Safety

The primary safety endpoint was the incidence of treatment-related serious adverse events (SAEs) that occur within 30 days of treatment procedure. Secondary safety outcomes included the incidence and severity of adverse events (AEs) that were assessed according to the National Cancer Institute Common Toxicity criteria (Version 3.0) after every TACE

Table 2 Cox Regression Of Independent Prognostic Factor For Overall Survival

	Cox Regression		P
	HR	95% CI	
Age (≤60, >60)	0.443	0.112–2.262	0.043
Gender (male, female)	1.746	0.842–6.561	0.442
Ps (0,1,2)			0.020
0	1	1	
1	3.461	0.562–5.561	
2	2.651	0.162–7.381	
Location of tumor (right, left, bilobar)			0.712
Right lobe	1	1	
Left lobe	0.471	0.082–8.461	
Bilobar	1.291	0.232–5.762	
Number of tumors (≤3, >3)	1.341	0.119–4.593	1.021
Lengths of the tumors (≤10cm, >10cm)	1.797	0.852–3.794	0.365
Metastasis	1.934	0.361–4.812	0.102
Child-Pugh (A, B)	0.734	0.084–7.568	0.341
CEA	3.281	1.452–7.409	0.477
CA199	1.571	0.458–6.451	0.737
AFP (≤200ng/mL, >200ng/mL)	0.973	0.584–1.621	0.916
Deposition of lipiodol			1.235
Mild	1	1	
Moderate	0.572	0.161–2.678	
Good	0.678	0.091–2.343	
Tumor response (PD,SD,PR,CR)			0.048
PD	1	1	
SD	0.783	0.303–2.123	
PR	1.237	0.462–1.461	
CR	0.982	0.562–1.732	
Number of sessions of TACE	0.650	0.274–1.129	0.157

Abbreviations: HR, hazard ratio; CI, confidence interval; PS, performance status; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; AFP, alpha-fetal protein; PD, alpha-fetal protein; SD, stable disease; PR, partial response; CR, complete response; TACE, transarterial chemoembolization.

cycle. If the treatment plan was terminated, all patients were assessed for their cumulative toxicities.

Statistical Analysis

For analyzing PFS and OS, all patients were followed up until disease progression, death or lost to follow-up. PFS and OS were calculated using Kaplan–Meier method. PFS was defined as the time between the first TACE procedure till disease progression, and OS was calculated from the date of the first TACE till death or last follow-up visit. Cox proportional-hazards regression model was used to assess the independent prognostic factors of OS. Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

Between April 15, 2014, and November 25, 2015, a total of 123 patients were recruited into the study (16 patients from Shandong Medical Imaging Research Institute, 7 from Shandong Cancer Hospital and Institute, 29 from Qilu Hospital of Shandong University, 25 from Affiliated Hospital of Qingdao University, 28 from Qingdao Central Hospital, 11 from 960 Hospital of People's Liberation Army, 5 from Qianfoshan Hospital of Shandong Province and 2 from People's Hospital of Jining City). The detailed baseline demographics and disease characteristics of the patients are shown in Table 1.

A total of 452 cycles of TACE with raltitrexed plus oxaliplatin were performed. Three patients completed 1

cycle of TACE, 120 patients completed at least 2 cycles of TACE (4 patients completed 2 cycles, 23 patients completed 3 cycles and 93 patients completed 4 cycles) and were evaluated for tumor response. Finally, 117 patients were followed up for PFS and OS.

Tumor Response

All 123 patients were evaluated for tumor response. Of these, 10 patients achieved a complete response (CR), 43 patients achieved a partial response (PR), 65 patients had stable disease (SD) and 5 patients had disease progression (PD). The objective response rate (ORR) was 43.09% and the disease control rate (DCR) was 95.5%.

PFS And OS

A total of 117 patients were subjected to follow-up. The median duration of follow-up was 20 months (ranging from 1.9 to 41.5 months). Twenty-two patients were alive on June 30, 2018, and were censored at that time point. The median PFS was 338 days (95% CI: 302, 704) (Figure 1). The median OS time was 623 days (95% CI: 461, 785) (Figure 2).

The Cox proportional-hazards regression model indicated that age, ECOG performance status and response to TACE were independent prognostic factors of OS (Table 2). Patients who achieved CR or PR after two cycles of TACE showed better OS than patients who achieved CR or PR after 4 cycles of TACE or sustained stable disease (SD) (Figure 3).

Safety

No treatment-related mortality occurred within 30 days of treatment procedure. The most common complications included post-embolization syndrome, liver dysfunction and hematological toxicity. No grade 4 adverse events occurred. The incidence of toxicity is summarized in Table 3.

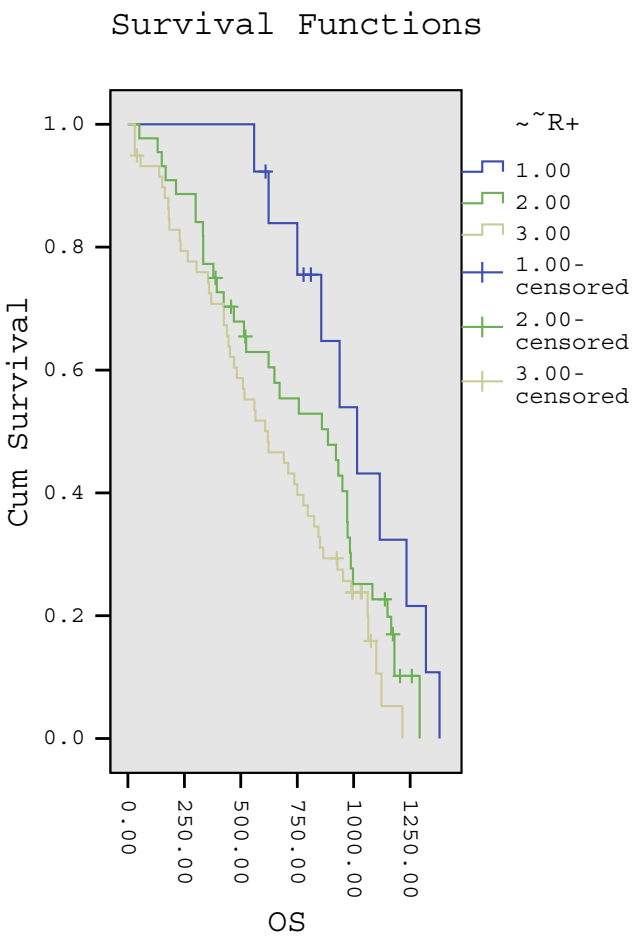

Figure 3 Kaplan – Meier curves generated for 117 patients to compare the median overall survival according to blue 1, CR or PR after 2 cycles of TACE, green 2, CR or PR after 4 cycles of TACE and yellow 3 SD after 4 cycles of TACE.

Discussion

HCC is the seventh most common cancer and third leading cause of cancer-related deaths worldwide.[14] Most of the HCC patients are diagnosed in the late stage and are not candidates for curative options such as liver transplantation and surgical resection. TACE is recommended as the mainstay treatment for patients with unresectable HCC. Raltitrexed can be administered as a short-term infusion or mixed with lipiodol, and so it is regarded as a better candidate for TACE when compared with 5-fluorouracil. A retrospective study showed that raltitrexed plus oxaliplatin regimen of TACE had a longer PFS time than traditional 5-fluorouracil-based TACE and was safe and tolerable in patients with unresectable HCC.[15] According to a prospective, multicenter, randomized study, raltitrexed-based TACE had a better disease control rate and the median OS and median PFS of raltitrexed-based TACE were significantly higher than those obtained by 5-fluorouracil-based TACE and doxorubicin-based TACE (OS: 13.4 vs. 9.6 vs. 8.5 months; PFS: 6.7 vs. 4.9 vs. 4.6 months).[16] The disease control rate of our study was similar to that of the previous study, but the median PFS and OS of our study are longer than those obtained in the previous study. We presumed that this might be due to the completion of more cycles of TACE in our study than the previous study. Majority of patients (i.e., 94%) in our study completed at least 3 cycles of TACE and three-fourths (75%) of patients completed 4 cycles of TACE when compared with those who completed 3 cycles of TACE (48%) in the previous study. Repeated TACE procedures can prolong OS in patients with unresectable HCC.[17,18] For patients who had PR or SD after a session of TACE, repeated TACE might

Table 3 Common Treatment-Related Adverse Events Occurred Among Entire Population

	AE	I n (%)	II n (%)	III n (%)	IV n (%)	Total n (%)
Hematological toxicity	RBC	32 (26.0%)	3 (2.4%)	0 (0.0%)	0 (0.0%)	35 (28.5%)
	WBC	29 (23.6%)	5 (4.1%)	1 (0.8%)	0 (0.0%)	35 (28.5%)
	HB	36 (29.3%)	5 (4.1%)	0 (0.0%)	0 (0.0%)	41 (33.3%)
	NEU	18 (14.6%)	4 (3.3%)	0 (0.0%)	0 (0.0%)	22 (17.9%)
	PLT	34 (27.6%)	6 (4.9%)	2 (1.6%)	0 (0.0%)	42 (34.1%)
Liver dysfunction	TBIL	28 (22.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	29 (23.6%)
	DBIL	31 (25.2%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	32 (26.0%)
	ALB	11 (8.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (8.9%)
	ALP	18 (14.6%)	8 (6.5%)	7 (5.7%)	0 (0.0%)	33 (26.8%)
	BUN	9 (7.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (7.3%)
	Cr	19 (15.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	19 (15.4%)
	ALT	34 (27.6%)	12 (9.8%)	5 (4.1%)	0 (0.0%)	51 (41.5%)
	AST	39 (31.7%)	8 (6.5%)	3 (2.4%)	0 (0.0%)	50 (40.7%)
Postembolization syndrome	Fever	95 (77.2%)	13(10.6%)	0 (0.0%)	0 (0.0%)	108 (87.8%)
	Abdominal pain	81 (65.9%)	8 (6.5%)	16 (13.0%)	0 (0.0%)	105 (85.4%)
	Nausea and vomiting	43 (35.0%)	16 (13.0%)	0 (0.0%)	0 (0.0%)	59 (48.0%)

Abbreviations: RBC, red blood cell; WBC, white blood cell; HB, hemoglobin; NEU, neutrophil; PLT, platelet; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; ALT, alanine transaminase; AST, aspartate transaminase.

give patients a chance to achieve CR or PR, or prevent rapid disease progression, prolonging the PFS.[19] However, Cox proportional-hazards regression model in the current study indicated that the number of TACE sessions was not an independent prognostic factor, while age, ECOG performance status and response to TACE were independent prognostic factors of OS. Sub-group analysis showed that patients who achieved CR or PR after 2 cycles of TACE had better OS than those who achieved CR or PR after 4 cycles of TACE and patients who sustained SD. The results of the current study achieved a tumor response rate at an early time point, predicting good survival benefit in patients with HCC undergoing TACE. This was in concordance with the results of the previous study.[20]

Our study also evaluated the safety and toxicity of raltitrexed plus oxaliplatin-based TACE in patients with unresectable HCC. No treatment-related mortalities occurred within 30 days of treatment procedure. The most common complications were similar with that of the traditional 5-fluorouracil and doxorubicin-based TACE. No grade 4 adverse events were observed. The results indicated that raltitrexed plus oxaliplatin-based TACE is safe and tolerable in patients with unresectable HCC.

Conclusion

Our study showed that raltitrexed plus oxaliplatin-based TACE led to high tumor response rate and promising PFS and OS, and was safe and tolerable in patients with unresectable HCC. This regimen might be a good choice for unresectable HCC patients treated with TACE.

Disclosure

The authors report no conflicts of interest in this work.

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