



Safety and efficacy of hepatic arterial infusion chemotherapy with raltitrexed and oxaliplatin post-transarterial chemoembolization for unresectable hepatocellular carcinoma

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ABSTRACT

Objective: To investigate the safety, efficacy, and prognostic factors of hepatic arterial infusion chemotherapy (HAIC) with raltitrexed and oxaliplatin post-transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (uHCC).

Methods: Thirty-seven patients with uHCC who received HAIC with raltitrexed and oxaliplatin post-TACE between June 2014 and December 2016 at our hospital were recruited. The primary endpoint was overall survival (OS), and secondary endpoint was progression-free survival (PFS). The overall response rate (ORR) was evaluated using the modified Response Evaluation Criteria in Solid Tumors. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (v4.0). The OS and prognostic factors were analyzed using the Kaplan–Meier method, log-rank test, and Cox regression models.

Results: Three (8.1%) patients achieved complete response, 17 (46.0%) patients achieved partial response, and the ORR was 54.0%. The median OS and median PFS were 19.0 months and 12.0 months, respectively. The common toxicities included grade 3–4 increased aspartate aminotransferase levels (8/37, 21.6%), grade 1–2 hyperbilirubinemia (75.7%, 28/37), nonspecific abdominal pain and fever, and grade 2–3 thrombocytopenia (18.9%, 7/37); no patients developed grade 3–4 neutropenia. Univariate analysis showed that the tumor diameter (≤ 50 mm, $p = 0.028$), Barcelona Clinic Liver Cancer (BCLC) stage ($p = 0.012$), hepatitis B virus DNA level ($p = 0.033$), and derived neutrophil-to-lymphocyte ratio (dNLR; derived neutrophils/leukocytes minus neutrophils) ($p = 0.003$) were predictive factors for prognosis. Multivariate analysis showed that patients with BCLC stage B disease ($p = 0.029$) and $dNLR \leq 2$ before therapy ($p = 0.004$) had better prognosis.

Conclusions: HAIC with raltitrexed and oxaliplatin post-TACE is a safe and efficacious therapy for patients with uHCC; in particular, those with BCLC stage B and $dNLR \leq 2$ have better prognosis.

Introduction

The mortality of hepatocellular carcinoma (HCC) is the second highest among cancers worldwide, and disease progression is the leading cause of death in patients with HCC.¹ In particular, in the Asia–Pacific region, the incidence of HCC and annual mortality rates related to HCC have increased during the past several years.²

Liver resection (LR) and liver transplantation (LT) are the first-line options for curative treatment; however, due to a shortage in donor livers for LT, LR is the main therapeutic modality.³ In addition, because

most patients have advanced-stage disease at the time of diagnosis, only 15% of patients with HCC can undergo surgery.⁴ Unfortunately, approximately 70% of patients experience recurrence within five years, and the prognosis of HCC is poor.⁵

Transarterial chemoembolization (TACE) is the first-line treatment for unresectable HCC (uHCC), especially for tumors with a diameter > 3 cm or for multifocal lesions (> 3) that do not exhibit vascular invasion or extrahepatic metastasis.⁶ Many reports indicate that TACE is a safe and efficacious regimen for patients with uHCC; TACE is associated with lower mortality and a shorter hospital stay than those associated

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with other treatment modalities.⁷ The drugs used in TACE are fluorouracil (5-FU), doxorubicin (DOX), and oxaliplatin⁸. Some reports have indicated that TACE with raltitrexed and oxaliplatin is safe and confers fewer adverse effects (AEs) in patients with uHCC. The median overall survival (mOS) and median progression-free survival (mPFS) are longer in patients receiving raltitrexed than in patients receiving 5-FU and DOX (mOS: 13.4–7.4 vs. 8.5–5.8 months; mPFS: 6.7–3.6 vs. 4.6–2.6 months). Increased aspartate aminotransferase levels (78.9% vs. 81.3%) and abdominal pain (68.4% vs. 78.7%), are also lower in those receiving raltitrexed TACE than in those receiving 5-FU and DOX TACE.^{8,9} The efficacy of TACE for massive uHCC lesions (≥ 10 cm) or those with vascular invasion or widespread nodules is not satisfactory; however, hepatic arterial infusion chemotherapy (HAIC) may still be effective.^{10,11} For some patients with uHCC that is resistant to TACE, HAIC may be effective.¹² Researchers have reported that HAIC with 5-FU, mitoxantrone, and cisplatin has significant efficacy for uHCC; the mOS is 11.3–14.0 months and mPFS is 7.0–7.7 months.^{13,14} Some researchers have reported that HAIC with raltitrexed and oxaliplatin for liver metastasis of colorectal cancer is associated with less toxicity, longer overall survival (OS), and longer progression-free survival (PFS) than those associated with HAIC with other drugs for uHCC. HAIC with raltitrexed and oxaliplatin remains feasible and promising, even after the failure of irinotecan and oxaliplatin for patients with liver metastasis of colorectal cancer.^{15,16} TACE is an effective approach for uHCC, and HAIC with raltitrexed and oxaliplatin post-TACE in patients with uHCC has been rarely reported. The present study's aim was to evaluate the safety, efficacy, and prognostic factors of HAIC with raltitrexed and oxaliplatin post-TACE in patients with uHCC.

Methods

Forty patients were diagnosed with uHCC based on pathological or radiological findings between December 2014 and September 2016 at our center; 3 patients were lost to follow-up, and 37 patients were included in the study. All patients satisfied the following criteria:¹ Child–Pugh class A or B disease, white blood cell count $> 2 \times 10^9/L$, neutrophil count $> 1 \times 10^9/L$, and platelet count $> 50 \times 10^9/L$;² total bilirubin $< 50 \mu\text{mol/L}$ and serum creatinine $< 2 \text{ mg/dL}$;³ unresectable tumors or tumors unsuitable for local ablation therapy;⁴ Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and⁵ no past history of treatment with raltitrexed.

The exclusion criteria were as follows:¹ other histological tumors;² unstable angina or severe heart failure;³ uncontrollable infection (grade > 2 infections; infections requiring antibiotic, antifungal, or antiviral interventions; infections requiring radiological or surgical interventions; infections with life-threatening consequences; or infections requiring urgent interventions according to the Common Terminology Criteria for Adverse Events (CTCAE);⁴ pregnant or lactating; and⁵ severe allergy to contrast media or other medicines.

The chemoembolization treatments for all patients were performed using digital subtraction angiography (DSA) equipment in our hospital. DSA of the celiac, superior mesenteric, and splenic arteries was performed to evaluate the hepatic arterial anatomy and tumor blood supply.

A 2.7-F microcatheter was advanced coaxially through an external catheter to select the tumor arteries. Subsequently, 40 mg of emulsified epirubicin (EPI, Main Luck Pharmaceutical, Shenzhen, China) and lipiodol (total volume < 20 ml; Lipiodol, Laboratoire Andre Guerbet, Aulnay-sous-Bois, France) were injected to embolize the tumor arteries; for some large tumors, polyvinyl alcohol particles were used to embolize the tumor arteries. If there was extrahepatic parasitic blood supply to the tumor (for example, from the left gastric, right phrenic, or right adrenal artery), chemoembolization was recommended after selective catheterization via the parasitic artery. If the microcatheter tip was near the gastroduodenal or right gastric artery, microcoil embolization was performed to avoid drug flow into the arteries of the gastrointestinal tract to protect the gastrointestinal tract.

The microcatheter was externally connected to an arterial infusion pump (Model LP 2000-P2) in the ward, and oxaliplatin (85 mg/m², Hengrui Medicine Co., Ltd., Jiangsu, China) was administered intra-arterially for 0–4 h; raltitrexed (3 mg/m², Tianqing Pharmaceutical Co., Ltd., Nanjing, China) was administered for approximately 1 h.¹⁷ HAIC post-TACE was regularly performed every 4–6 weeks. The endpoint was death or Child–Pugh class C disease. Enhanced computed tomography (CT) or magnetic resonance imaging (MRI) and laboratory tests (blood routine examination, biochemical tests, measurement of alpha-fetoprotein levels, coagulation testing) were regularly performed before therapy; patients were followed up until death or until they were lost to follow-up. The overall response rate (ORR) was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST), and AEs were evaluated using the CTCAE v4.0.

Statistical analysis

OS was calculated from the date of the first HAIC post-TACE treatment to the date of death or until the date on which the patient was considered lost to follow-up. PFS was defined from the date of the first HAIC treatment to the date of tumor progression. PFS and OS were estimated using the Kaplan–Meier method, and univariate analyses were performed using the log-rank test. Multivariate analysis was performed using Cox proportional hazards models. All analyses were performed with SPSS version 22.0 (IBM Corp., Armonk, NY, United States SPSS version 22.0), and a P -value < 0.05 was considered statistically significant.

Results

Baseline characteristics of patients

Details of the characteristics of the 37 patients who were treated with HAIC with raltitrexed and oxaliplatin post-TACE are shown in [Table 1](#). The mean age was 57.2 years (ranging from 32 to 81 years). The sex ratio (female to male) was 4:33. Most patients had hepatitis B virus (HBV)-related disease (33, 89.2%), and 13 patients (33.3%) had HBV DNA levels $> 10^2$ copies/mL. Twenty-seven patients (81.2%) had an ECOG status of 0, and 9 (27.3%) patients had an ECOG status of 1. Seventeen patients (45.9%) had Barcelona Clinic Liver Cancer (BCLC) stage B disease, and 20 patients (54.1%) had BCLC stage C disease. Thirty (81.1%) patients had Child–Pugh class A disease, and the mean tumor diameter was 75.3 mm. Of all the patients, 21 patients (56.8%) had one solitary lesion and 8 (21.6%) had vascular invasion. 4 patients (10.8%) had extrahepatic metastases; 3 had lung metastases, and 1 patient had adrenal and bone metastases.

Safety

There were no procedure-related deaths in the present study. Common AEs included nausea and vomiting (48.6%), grade 3–4 increased aspartate aminotransferase levels (21.6%, 8/37), grade 1–2 hyperbilirubinemia (75.7%, 28/37), grade 1–2 pain (32.4%), grade 1 fever (37.8%, 14/37), and grade 2–3 thrombocytopenia (18.9%, 7/37). No patients developed neutropenia or other serious complications ([Table 2](#)).

Survival

The median follow-up period was 34 months, and the OS of the 37 patients was 19.0 months ([Fig. 1](#)). The mOS of patients with BCLC stage B and BCLC stage C uHCC were 34 months and 13 months, respectively ($p = 0.012$). In the present study, the PFS was 12.0 months; the mPFS of patients with BCLC stage B uHCC was 17 months and that of patients with BCLC stage C uHCC was 8 months ($p = 0.054$). The 6-, 12-, and 24-month mOS rates were 84%, 64%, and 41%, respectively ([Fig. 1](#)). The tumor response rates were as follows: complete response (CR) was achieved in

Table 1
Baseline characteristics.

Baseline characteristics	Value
Age, years	
>60	20 (54.1%)
≤60	17 (45.9%)
Sex	
Male	33 (89.2%)
Female	4 (10.8%)
Diameter (mm)	
<50	13 (35.1%)
50–100	8 (21.6%)
≥100	16 (43.3%)
Child–Pugh stage	
A	30 (81.1%)
B	7 (18.9%)
BCLC	
B	17 (45.9%)
C	20 (54.1%)
ECOG performance status	
0	27 (73.0%)
1	9 (24.3%)
2	1 (2.7%)
Tumor nodules	
Solitary	16 (43.2%)
Multiple	21 (56.8%)
Vascular invasion	
With	8 (21.6%)
Without	29 (78.4%)
Extrahepatic metastasis	
With	4 (10.8%)
Without	33 (89.2%)
HBV infection	
Yes	33 (89.2%)
No	4 (10.8%)
HBV DNA level >2 × 10 ³ copies/mL	
Yes	13 (33.3%)
No	24 (66.7%)
Cirrhosis	
With	32 (86.5%)
Without	5 (13.5%)
AFP	
≤400 ng/ml	27 (73.0%)
>400 ng/ml	10 (27.0%)
dNLR ^a ≤2	
Yes	17 (45.9%)
No	20 (54.1%)

AFP: alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HBV: hepatitis B virus; dNLR: derived neutrophil-to-leukocyte ratio.

^a dNLR = leukocyte/(absolute leukocyte count - absolute neutrophil count).

Table 2
Observed toxicity according to the CTCAE.

	Severity grade	Value
Hematological		
Thrombocytopenia	2–3	7 (18.9%)
Neutropenia	3–4	0 (0.0%)
Non-hematological		
Elevation of liver enzymes	3–4	8 (21.6%)
Elevation of bilirubin	1–2	28 (75.7%)
Nausea/vomiting	1–2	18 (48.6%)
Pain	1–2	12 (32.4%)
Fever	1	14 (37.8%)

Toxicity was assessed according to the CTCAE v.4.0 criteria. CTCAE, Common Terminology Criteria for Adverse Events.

8.1% (3/37) of patients, and partial response (PR) was achieved in 46.0% (17/37) of patients (Table 3).

Twelve prognostic factors were analyzed univariately, and four prognostic variables were identified (Table 4). Univariate analysis showed that the tumor diameter (≤50 mm, p = 0.028), BCLC stage

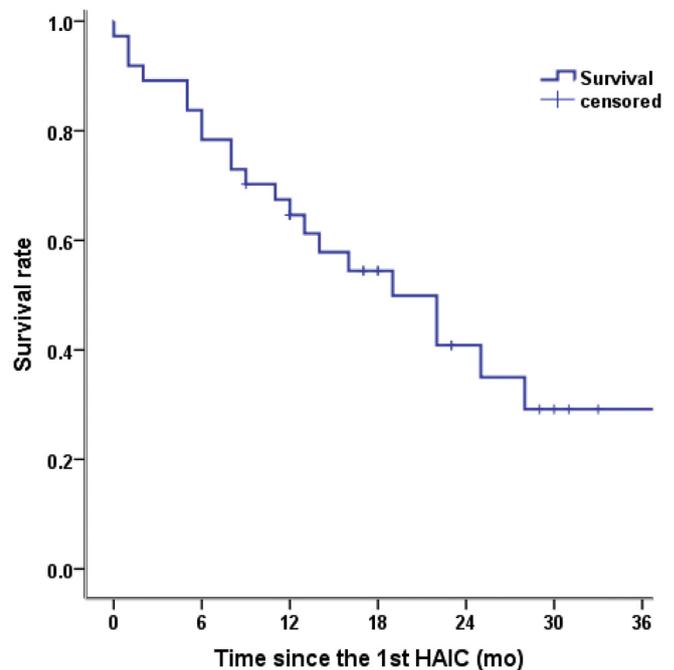


Fig. 1. Kaplan–Meier survival curves for patients receiving HAIC with raltitrexed and oxaliplatin post-TACE. HAIC: hepatic arterial infusion chemotherapy; TACE: transarterial chemoembolization.

(p = 0.012), HBV DNA level (p = 0.033), and derived neutrophil-to-lymphocyte ratio (dNLR; derived neutrophils/leukocytes minus neutrophils) (p = 0.003) were predictive factors for prognosis. In multivariate analysis, BCLC stage (p = 0.029, Fig. 2) and adNLR ≤ 2 (p = 0.004, Fig. 3) were significant factors for patient survival after HAIC with raltitrexed and oxaliplatin post-TACE (Fig. 3).

In a 53-year-old man with HCC (Case 1, Fig. 4), pre-operative MRI revealed a lesion in the liver (Fig. 4A). Angiography via the proper hepatic artery revealed a tumor stain in the liver (Fig. 4B). Post-operative CT revealed scattered deposition of lipiodol within the lesions in the liver (Fig. 4C). After 4 weeks, angiography via the proper hepatic artery revealed scattered deposition of lipiodol within the lesions in the liver (Fig. 4D).

Discussion

HAIC has been used for advanced HCC in Southeast and East Asian countries and is a safe and efficacious treatment for uHCC. In the present study, HAIC with raltitrexed and oxaliplatin in post-TACE were evaluated.

Raltitrexed and oxaliplatin are safe and efficient drugs for liver metastasis of colorectal cancer. The safety and efficacy of HAIC for uHCC have also been explored previously.^{15,16} In prior studies of efficacy and survival data for patients with uHCC who received HAIC with 5-FU, mitoxantrone, and cisplatin, the mOS ranged from 6.0 to 14.0 months, ORR ranged from 16.7% to 45.6%, and mPFS ranged from 3.6 to 7.7 months; these results are unsatisfactory. In some reports, HAIC post-TACE for uHCC has been suggested to be effective and confer longer OS and PFS than those associated with TACE alone.^{17,18} Thus, the current study evaluated the use of HAIC with raltitrexed and oxaliplatin for uHCC post-TACE. In the present study, the mOS after HAIC post-TACE was 19.3 months; the advantages of HAIC with raltitrexed and oxaliplatin compared with HAIC with 5-FU, mitoxantrone, and cisplatin (OS: 6–14 months) are obvious. The ORR in our study was 54%, which is higher than that reported by previous studies (15.7–45.6%) that evaluated HAIC with 5-FU, mitoxantrone, and cisplatin. The mPFS in our study was 12.0 months, which is also higher than that revealed in prior studies (3.6–7.7 months).^{19,20}

Table 3

Tumor response according to the mRECIST.

Outcome	HAIC with raltitrexed and oxaliplatin post-TACE
DCR ^a	75.7% ²⁸
ORR ^b	54.1% ²⁰
CR	8.1% ³
PR	46.0% ¹⁷
SD	21.6% ⁸
PD	24.3% ⁹

mRECIST: modified Response Evaluation Criteria in Solid Tumors; DCR: disease control rate; ORR, overall response rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

^a DCR was calculated as CR + PR + SD.

^b ORR was calculated as CR + PR.

Table 4

Univariate and multivariate analyses of predictors of overall survival.

Characteristic	Univariate (p*-value)	Multivariate (p*-value)	HR	95% CI
Age (≤65 y)	0.276			
Sex	0.395			
Diameter (≤50 mm)	0.028			
Child–Pugh stage	0.789			
BCLC	0.012	0.029	3.080	1.122–8.455
ECOG performance status	0.183			
Tumor nodules	0.159			
Vascular invasion	0.064			
HBV DNA level	0.033			
>2 × 10 ³ copies/mL				
Cirrhosis	0.759			
AFP	0.544			
dNLR ^a ≤2	0.003	0.004	0.020	0.064–0.599

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; dNLR, derived neutrophil-to-leukocyte ratio; HR, hazard ratio; CI, confidence interval.

^a dNLR = leukocyte/(absolute leukocyte count - absolute neutrophil count); * < 0.05.

The advantages of TACE with raltitrexed and oxaliplatin for uHCC compared with TACE with 5-FU, EPI, and oxaliplatin have been shown in previous studies; the OS ranged from 7.4 to 13.4 months, mPFS ranged from 3.6 to 6.7 months, and ORR (CR + PR) ranged from 2.5 to 67.2%.^{8,9} In the present study, the mOS was 19.3 months, mPFS was 5.0 months, and ORR was 54.1%. HAIC with raltitrexed and oxaliplatin post-TACE may prolong patient survival and has a higher disease control rate than that associated with TACE alone with raltitrexed and oxaliplatin, but more data need to be collected.

There were a similar number of AEs noted in the present study compared to that in previous studies of HAIC with 5-FU, mitoxantrone, and cisplatin (nausea and vomiting (60.0–71.4%), abdominal pain (68.4%), increased serum liver enzymes (59.5–78.9%), leukopenia (36.0–37.1%), neutropenia (35–39%), and thrombocytopenia (19–38.1%)).^{8–10,21,22} One study revealed that the rate of AEs was significantly lower in patients treated with HAIC with a combination of 5-FU, leucovorin, and oxaliplatin than in those treated with TACE among patients with massive uHCC; in particular, the liver dysfunction rate among patients in the HAIC group was significantly lower than that among patients in the TACE group (p < 0.001).¹⁰ Some studies have also demonstrated that the rates of embolization complications after HAIC were lower than those after TACE.^{13,20,23} Another study showed that there were no significant differences in overall AEs after raltitrexed- and oxaliplatin-based, fluorouracil- and oxaliplatin-based, and DOX- and oxaliplatin-based TACE.⁸ Raltitrexed- and oxaliplatin-based TACE may not increase toxicity. HAIC with raltitrexed and oxaliplatin may be safer than TACE with raltitrexed and oxaliplatin or HAIC with 5-FU,

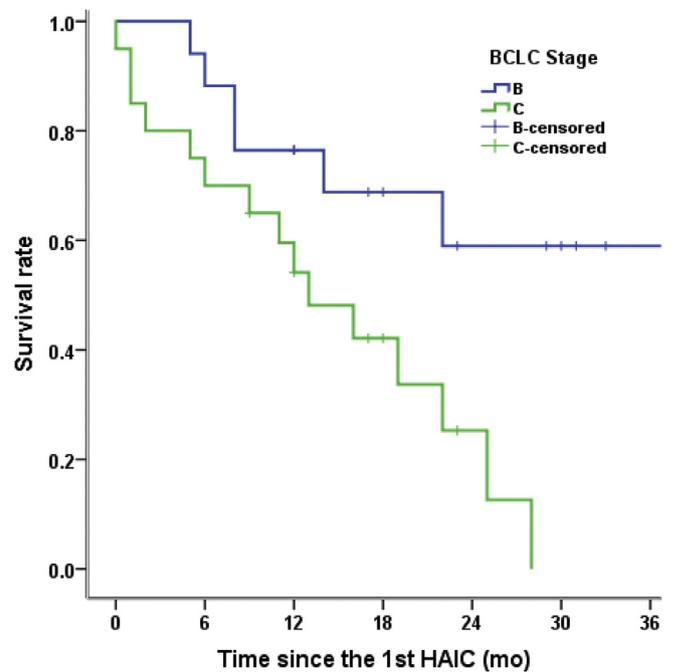


Fig. 2. Kaplan–Meier survival curves for patients receiving HAIC with raltitrexed and oxaliplatin post-TACE. P-value based on a log-rank test. The BCLC stage is associated with OS (P = 0.012). HAIC: hepatic arterial infusion chemotherapy; BCLC: Barcelona Clinic Liver Cancer; OS: overall survival.

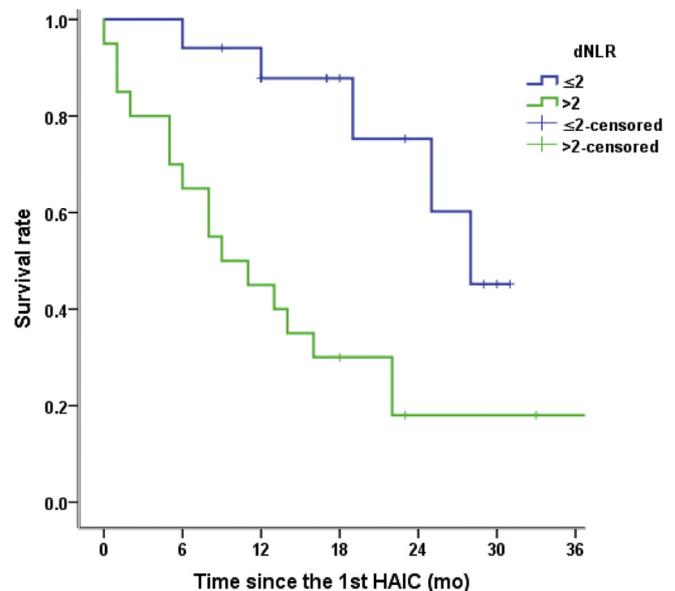


Fig. 3. Kaplan–Meier survival curves for patients receiving HAIC with raltitrexed and oxaliplatin post-TACE. P-value based on a log-rank test. dNLR = leukocyte/(absolute leukocyte count minus absolute neutrophil count) (P = 0.003). HAIC: hepatic arterial infusion chemotherapy; TACE: transarterial chemoembolization; dNLR: derived neutrophil-to-lymphocyte ratio.

mitoxantrone, and cisplatin. In conclusion, HAIC with raltitrexed and oxaliplatin post-TACE is safe.

In previous studies, HBV DNA levels were significantly correlated with liver function exacerbation after TACE or partial hepatectomy.^{24,25} However, researchers have reported that high HBV DNA levels before TACE (≥2 × 10³ copies/mL) reduce mOS, but do not affect hepatic failure-related mortality.²⁶ If these patients do not undergo antiviral therapy, they have an increased risk of reactive HBV after hepatectomy

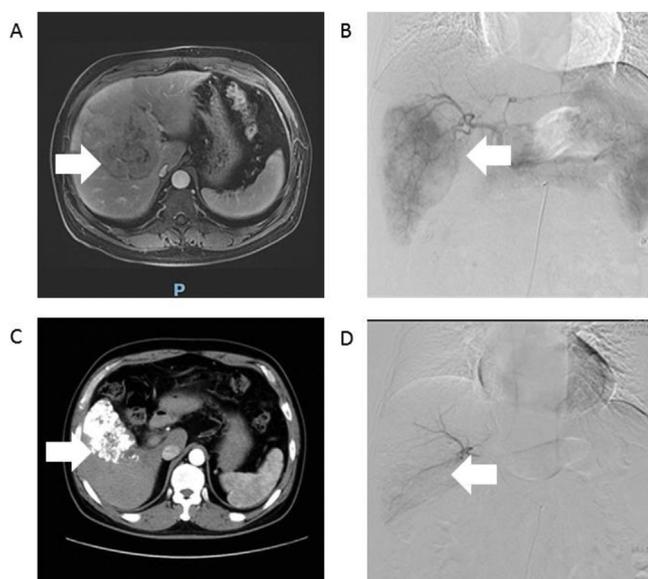


Fig. 4. Images of case 1. A: Pre-operative MRI revealed the lesion in the liver (as indicated by the arrow). B: Angiography via the proper hepatic artery revealed a tumor stain in the liver (as indicated by the arrow). C: Post-operative CT revealed scattered deposition of lipiodol within the lesions in the liver (as indicated by the arrow). D: After 4 weeks, angiography via the proper hepatic artery revealed scattered deposition of lipiodol within the lesions in the liver (as indicated by the arrow). MRI: magnetic resonance imaging; CT: computed tomography.

or TACE.²⁴ Asia-Pacific clinical practice guidelines have highlighted that HBV viral load is associated with recurrence after radical treatment of HCC. In one report, patients with HCC with hepatitis B surface antigen levels >250 IU/mL prior to curative resection had an increased risk of late recurrence compared with those with lower viral loads.²⁷ Moreover, the outcome of HBV DNA levels correlated with OS was observed in the present study, and high HBV DNA levels before therapy may confer poor OS in patients with uHCC. High HBV DNA levels may induce HCC progression. Antiviral therapy for HBV may be crucial in patients with HBV-related HCC to prevent recurrence and improve survival.

Multivariate analysis revealed that a dNLR ≤ 2 was an independent risk factor associated with OS. Many previous studies have demonstrated that the dNLR is related to immune function and inflammation. The dNLR has been shown to be associated with outcomes in various cancer entities. For instance, previous studies have shown that in patients with melanoma, those with a dNLR > 3 have shorter time to progression (TTP) and OS. Another study showed that in patients with colon cancer, those with a dNLR ≤ 3 had longer TTP than those with a dNLR > 3 ($p < 0.001$) and that those with a dNLR ≤ 2.2 had long OS ($p = 0.018$).^{28,29} In patients with melanoma, the baseline dNLR was associated with prognosis in patients with metastatic melanoma receiving ipilimumab.³⁰ Studies of HCC have led to similar conclusions. The dNLR is an independent prognostic factor for OS; a dNLR ≥ 1.8 predicts poor prognosis in patients with HBV-associated HCC after TACE.^{31,32} In a study of patients with uHCC treated with HAIC, those with a dNLR < 2.87 had longer PFS and OS.³³ The limitation of all these studies is that none have used consistent values for the dNLR. The importance of the dNLR in HCC or other cancers should be further investigated.

The present study also found that BCLC stage CHCC was an independent risk factor associated with OS in the multivariate analysis. Patients with BCLC stage B HCC had longer OS than those with BCLC stage C HCC ($p = 0.011$). The mOS times for patients with BCLC stage B and C HCC were 34 months and 13 months, respectively, and the mPFS times were 12.0 months and 6.0 months, respectively. Currently, the BCLC stage system is recommended in many guidelines. Some studies have shown that patients with BCLC stage B HCC have obviously improved prognosis;

those with substage B1 HCC have a longer OS than those with substage B2, B3, or B4 HCC (33.0 months vs. 20.8 months vs. 16.1 months vs. 22.2 months, $p = 0.003$).³⁴ One study revealed that a new subclassification of BCLC stage C HCC (C0, C1, C2, C3, and C4) had significant differences ($p < 0.001$) when different treatment modalities were selected for patients within each substage of disease.³⁵ The sample size in the present study was too small to classify patients with different substages of BCLC stage B or CHCC.

In this retrospective study, the safety and effectiveness of HAIC with raltitrexed and oxaliplatin were demonstrated in patients with uHCC. The limitations of this study were the limited sample size and single-arm retrospective study design. Compared to previous reports, the outcomes were favorable. In addition, the sample size was limited; thus, some bias was difficult to avoid. More detailed data and multicenter cooperation are needed to demonstrate the advantages of HAIC with raltitrexed and oxaliplatin post-TACE in patients with uHCC.

Conclusion

HAIC with raltitrexed and oxaliplatin post-TACE is a safe and efficacious therapy in patients with uHCC, and this treatment may provide new clues for clinical practice. In the present study, BCLC stage B and dNLR ≤ 2 were independent risk factors associated with OS.

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