Hepatic arterial infusion of oxaliplatin plus raltitrexed in unresectable hepatocellular carcinoma with or without portal vein tumour thrombosis

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Abstract

Background Unresectable hepatocellular carcinoma (HCC) has a poor prognosis. According to the HCC management guidelines in China, the standard treatment of Barcelona Clinic Liver Cancer (BCLC) stage B or C HCC with portal vein tumour thrombosis (PVTT) is chemoembolization. However, some patients with BCLC stage B or C HCC with PVTT respond poorly to chemoembolization. We aimed to compare tumour responses and survival benefits between patients with unresectable HCC with or without PVTT.

Methods We reviewed 119 consecutive patients with unresectable HCC with PVTT (n = 67) and without PVTT (n = 52) who underwent hepatic arterial infusion of oxaliplatin plus raltitrexed between January 2018 and April 2021. Overall survival, progression-free survival, tumour responses, and adverse events were compared between the groups.

Results There were no significant between-group differences in the objective response rates and median progression-free survival. The median overall survival was significantly longer in the group without PVTT than in that with PVTT (17.0 vs 10.4 months, respectively; P = 0.024).

Conclusion Hepatic arterial infusion of oxaliplatin plus raltitrexed may be efficacious in patients with unresectable HCC with or without PVTT.

Key words: hepatic arterial infusion; hepatocellular carcinoma; oxaliplatin; portal vein tumour thrombosis; raltitrexed

Introduction

Liver cancer is the fourth most common cancer in China [1], with hepatocellular carcinoma (HCC) accounting for >90% of liver cancer cases [2]. In China, approximately 64% of HCC cases are Barcelona Clinic Liver Cancer (BCLC) stage B or C at diagnosis [3]. According to the HCC management guidelines in China [4], the standard treatment for BCLC stage B or C HCC with portal vein tumour thrombosis (PVTT) is chemoembolization.
However, some patients with BCLC stage B or C HCC with PVTT respond poorly to chemoembolization [5].

Previous studies reported that patients with HCC who are treated with hepatic arterial infusion chemotherapy (HAIC) have a high response rate and this response translates into survival benefits [6, 7]. Unlike systemic chemotherapy, HAIC involves the direct delivery of chemotherapeutic agents into tumour-supplying arteries, thus increasing their local concentration [8] and achieving better antitumour efficacy. Systemic toxicity is limited due to the agents’ first pass effect through the liver [9]. According to the Japanese HCC management guidelines [10], HAIC is recommended for BCLC stage B HCC that is refractory to transcatheter arterial chemoembolization (TACE) and BCLC stage C HCC with PVTT. Moreover, HAIC is usually the first-line treatment option for patients with HCC with PVTT in Japan [6].

In a previous phase II clinical trial [11], we showed that hepatic arterial infusion of oxaliplatin plus raltitrexed (HAI-OR) was effective and safe in patients with intermediate-stage or advanced-stage HCC. However, it is unclear which subgroup of patients with unresectable HCC with and without PVTT would benefit more from HAI-OR. Here, we aimed to classify patients with unresectable BCLC stage B or C HCC according to the PVTT status and compare tumour responses between the groups and to determine which patients were most suitable for HAI-OR.

Patients and methods

Research ethics and patient consent

All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study design was approved by the ethics committee of Fujian Medical University Cancer Hospital (Fujian, China) (K2022-034-01). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Study design and population

Between January 2018 and April 2021, 156 consecutive patients with unresectable HCC who were treated with HAI-OR at our institution were screened. The patients with extrahepatic spread or those who were treated with HAI-OR and systemic therapy were excluded. We selected patients with BCLC stage B HCC with TACE refractoriness (defined as an ineffective response to two or more consecutive TACE procedures) [12] or BCLC stage C HCC with PVTT. Thus, 52 patients with BCLC stage B HCC (HCC-without-PVTT group) and 67 with BCLC stage C HCC (HCC-with-PVTT group) were included in the intention-to-treat population. Twelve patients were excluded from the intention-to-treat population for not following the planned post-treatment efficacy assessment. Twenty-one patients were excluded from the per-protocol population for not following the planned survival analysis (Figure 1). The last follow-up date was 18 June 2021.

A multidisciplinary team of surgeons, interventional oncologists, radiologists, and oncologists identified patients with unresectable HCC. Complying with the recommendation of the American Association for the Study of Liver Diseases [13], the diagnosis of HCC was confirmed by pathology, contrast-enhanced computed tomography, or magnetic resonance imaging. Six patients (5.0%) were diagnosed by pathology through core needle biopsy and 12 patients (10.1%) were diagnosed pathologically after resection. The eligibility criteria were (i) age 18–75 years, (ii) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, (iii) Child–Pugh liver function class A or B, (iv) adequate haematological cell counts (white blood cell count ≥3,000/mm³, absolute neutrophil count ≥1,500/mm³, and platelet count ≥75,000/mm³), (v) adequate renal function (serum creatinine ≤1.5 × the upper limit of normal), and (vi) life expectancy of ≥2 months. We excluded patients who had (i) received any previous systemic therapy, (ii) received any local treatment over the preceding 4 weeks, and/or (iii) showed extrahepatic spread.

Treatment protocol

The HAIC procedure was performed using the Seldinger technique to puncture the femoral artery. Using digital subtraction angiography, a catheter and coaxial microcatheter were inserted into the feeding hepatic artery (Supporting Information). The treatment regimen involved oxaliplatin (100 mg/m² continuously over 4 hours) and raltitrexed (3 mg/m² continuous infusion over 1 hour). After HAIC, the catheter and sheath were removed. The treatment was divided into 3-week cycles and discontinued in case of disease progression, intolerable toxicity, or treatment refusal.

Whenever a patient experienced grade 3 or 4 toxicity during treatment, the next treatment cycle was suspended until the patient’s toxicity grade was decreased to grade ≤1. Treatment was resumed, with the dosage of both chemotherapy agents reduced by 25%.

Outcomes

Tumour response was assessed using abdominal computed tomography or magnetic resonance imaging every 6 weeks, according to the Response Evaluation Criteria in Solid Tumours (version 1.1) [14]. In patients with suspected extrahepatic spread, further examinations were performed. The primary endpoint was objective response rate (ORR), calculated as the proportion of patients who achieved a complete or partial response. The secondary endpoints were overall survival (OS), defined as the time from initiating the first HAIC procedure to the date of death from any cause or the last follow-up; progression-free survival (PFS), calculated from the initiation of the first HAIC procedure to the date of disease progression or death from any cause or the last follow-up; and treatment-related adverse events, assessed using Common Terminology Criteria for Adverse Events v4.0 [15].

Statistical analyses

ORRs were calculated for the intention-to-treat and per-protocol populations. The intention-to-treat population comprised patients who underwent at least one cycle of HAIC. The per-protocol population comprised patients who met the eligibility criteria and underwent one or more efficacy assessments after treatment.

Because this was a retrospective study of consecutive patients at a single centre, a sample-size calculation was not performed. Quantitative data were analysed using an independent-sample t-test for intergroup comparisons, while categorical data were assessed using the chi-square test. OS and PFS were estimated using the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were conducted using SPSS software (version 18.0) (SPSS Inc., Chicago, IL, USA). Statistical significance was set at a P-value of <0.05.
Results

Patient baseline characteristics

The mean age was 55.4 ± 9.9 and 53.4 ± 10.6 years for the HCC-without-PVTT and HCC-with-PVTT groups, respectively. The HCC-without-PVTT group had 51 men and 1 woman, while the HCC-with-PVTT group had 61 men and 6 women. No patient had a history of alcohol addiction or hepatitis C virus infection. There were no significant differences at baseline between the two groups (Table 1). The median follow-up duration was 9.0 (interquartile range, 4.9–15.3) months in the HCC-without-PVTT group and 9.4 (interquartile range, 5.6–12) months in the HCC-with-PVTT group.

Tumour response

Tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours (version 1.1) (Table 2). One patient in the HCC-without-PVTT group and no patients in the HCC-with-PVTT group achieved complete response. The ORRs of intention-to-treat and per-protocol populations were 23/52 (44.2%) and 23/47 (48.9%), respectively, in the HCC-without-PVTT group and 26/67 (38.8%) and 26/60 (43.3%), respectively, in the HCC-with-PVTT group. There was no significant difference in the ORR of intention-to-treat or per-protocol populations between the two groups (P = 0.578 and P = 0.696, respectively).
Cycles of HAIC, mean ± SD

Patients, n 52 67
Gender, n (%)
Male 51 (98.1) 61 (91.0) 0.135
Female 1 (1.9) 6 (9.0) 5
Age (years), mean ± SD 55.4 ± 9.9 53.4 ± 10.6 0.236
HBsAg expression
Positive, n (%) 48 (92.3) 65 (97.0) 0.402
Negative, n (%) 4 (7.7) 2 (3.0) 5
Child–Pugh class
A, n (%) 42 (80.8) 44 (65.7) 0.098
B, n (%) 10 (19.2) 23 (34.3) 0.036
ECOG score
0 20 (38.5) 29 (43.3) 0.484
1 29 (55.8) 31 (46.3) 2
2 3 (5.8) 7 (10.4) 5
AFP, ng/ml
>400, n (%) 32 (61.5) 47 (70.1) 0.336
≤400, n (%) 20 (38.5) 20 (29.9) 5
Maximum tumour size, cm
>10, n (%) 17 (32.7) 30 (44.8) 0.192
≤10, n (%) 35 (67.3) 37 (55.2) 1
Number of HCC foci
≤3, n (%) 9 (17.3) 17 (25.4) 0.373
>3, n (%) 43 (82.7) 50 (74.6) 0.2
Portal vein tumour thrombosis grade
Vp1-2, n (%) 11 (16.4) 2
Vp3, n (%) 29 (43.3) 2
Vp4, n (%) 27 (40.3) 2
Cycles of HAIC, mean ± SD 3.0 ± 1.5 3.4 ± 1.7 0.114
Previous therapy
Resection 8 4
Ablation 8 2
TACE 52 16
Radiotherapy 4 1
Supplementary therapy
Systemic treatments 7 7
Sorafenib 3 3 0.775
Lenvatinib 0 3
Apatinib 3 0
Regorafenib 0 1
Anlotinib 1 0
PD-1 monoclonal antibody 3 1
Locoregional treatments 1 3
Resection 0 1
Ablation 1 1 0.631
Radiotherapy 0 1

**Survival analysis**

The median PFS was 5.8 (95% confidence interval [CI], 4.5–7.1) months in the HCC-without-PVTT group and 5.5 (95% CI, 4.3–6.7) months in the HCC-with-PVTT group. There was no significant difference in the median PFS between the two groups ($P = 0.897$) (Figure 2).

The median OS was 17.0 (95% CI, 12.4–21.6) months in the HCC-without-PVTT group and 10.4 (95% CI, 8.5–12.3) months in the HCC-with-PVTT group. The median OS in the HCC-without-PVTT group was significantly longer than that in the HCC-with-PVTT group ($P = 0.024$) (Figure 3).

**Adverse events**

No treatment-related death was observed in either group. The most common adverse events were hematologic toxicity, liver dysfunction, abdominal pain, fever, and gastrointestinal reaction in the two groups (Table 3). Grade 3 and 4 leukopenia and grade 3 anemia occurred in one (1.5%) patient in the HCC-with-PVTT group. Grade 3 elevated alanine aminotransferase occurred in one (1.5%) patient in the HCC-without-PVTT group. Grade 3 elevated aspartate aminotransferase were observed in three (5.8%) and two (3.0%) patients in the HCC-without-PVTT group and the HCC-with-PVTT group, respectively. There were no significant differences at adverse events between the two groups.

**Discussion**

We compared the efficacy of HAI-OR in patients with unresectable HCC without PVTT with TACE refractoriness and those with unresectable HCC with PVTT. The HCC-without-PVTT group had a significantly longer median OS than the HCC-with-PVTT group. Although the HCC-without-PVTT group had a longer median PFS and a higher ORR, the differences were not statistically significant.

Currently, oral sorafenib is the first-line treatment for unresectable HCC with PVTT. It is also the recommended alternative treatment for BCLC stage B HCC with TACE refractoriness, worldwide [16–18]. However, not all patients with unresectable HCC benefit from sorafenib. Some studies found that HAIC-based treatments led to better survival in patients with unresectable HCC with PVTT than in those who received sorafenib alone [19–21]. These findings suggest that sorafenib may not be the best treatment option for HCC with PVTT. Moreover, in Japan, HAIC (instead of sorafenib) is recommended as the first-line treatment option for patients with HCC with PVTT [10]. The Asian-Pacific SHARP trial showed that among patients with advanced HCC who were administered sorafenib, the median OS and ORR were 6.5 months and 3.3%, respectively [22]. In the present study, the median OS and ORR in patients with unresectable BCLC stage B and C HCC treated with HAI-OR were 17.0 and 10.4 months and 44.2% and 38.8%, respectively. Although our study was not a direct comparative study, our outcomes still indicated a promising prospect for HAI-OR as an alternative to sorafenib in patients with unresectable HCC.

HAIC was recently proven effective in a series of clinical trials conducted in Asia, especially in China [19, 20], and is therefore widely used to treat patients with unresectable HCC. Most of these studies were performed on patients with unresectable HCC with PVTT. Patients with BCLC stage B comprise a very diverse set of patients. Current recommendations include only TACE as a treatment option based on the BCLC staging system. Bolondi et al. [23] suggested sorafenib or other options—currently under clinical trials—for patients beyond the up-to-seven criteria. Moreover, according to the Japanese HCC management guidelines, HAIC is recommended for patients with BCLC stage B HCC with TACE refractoriness [10]. Our study compared

APF, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HBsAg, Hepatitis B surface antigen; PD-1, programmed cell death-1; PVTT, portal vein tumour thrombosis; SD, standard deviation; TACE, transcatheter arterial chemoembolization; Vp1, third-branch portal vein tumour thrombosis; Vp2, second-branch portal vein tumour thrombosis; Vp3, first-branch portal vein tumour thrombosis; Vp4, main portal vein tumour thrombosis.
tumour responses and survival benefits in patients with unresectable HCC between those with and without PVTT; all patients with unresectable HCC without PVTT had TACE refractoriness. The median OS was significantly longer in the HCC-without-PVTT group than in the HCC-with-PVTT group. Although there was no significant difference in the ORR and median PFS between the two groups, the median PFS was longer and the ORR was higher in the HCC-without-PVTT group than in the HCC-with-PVTT group.

Although HAIC is effective for HCC, the optimal HAIC regimen remains unknown due to various reported regimens of HCC treatment in practice, including single or combined administration of cisplatin, fluorouracil, doxorubicin, epirubicin, mitomycin C, and oxaliplatin [6]. For example, the three most common HAIC regimens used in Japan are (i) low-dose fluorouracil plus cisplatin, (ii) HAIC with interferon, and (iii) HAIC with cisplatin [24]. In our study, the ORRs of the intention-to-treat population in the HCC with and without PVTT groups were 38.8% and 44.2%, respectively. In previous studies that applied oxaliplatin, fluorouracil, and leucovorin in the treatment of tumour responses and survival benefits in patients with unresectable HCC between those with and without PVTT; all patients with unresectable HCC without PVTT had TACE refractoriness. The median OS was significantly longer in the HCC-without-PVTT group than in the HCC-with-PVTT group. Although there was no significant difference in the ORR and median PFS between the two groups, the median PFS was longer and the ORR was higher in the HCC-without-PVTT group than in the HCC-with-PVTT group.

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| Population | Treatment group | CR | PR | SD | PD | ORR (%) | P-value |
|------------|----------------|----|----|----|----|---------|---------|
| Intention-to-treat population | HCC-without-PVTT group (n = 52) | 1 | 22 | 15 | 9 | 23/52 (44.2) | 0.578 |
| | HCC-with-PVTT group (n = 67) | 0 | 26 | 24 | 10 | 26/67 (38.8) | |
| Per-protocol population | HCC-without-PVTT group (n = 47) | 1 | 22 | 15 | 9 | 23/47 (48.9) | 0.696 |
| | HCC-with-PVTT group (n = 60) | 0 | 26 | 24 | 10 | 26/60 (43.3) | |

CR, complete response; HCC, hepatocellular carcinoma; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; PVTT, portal vein tumour thrombosis.

Table 2. Objective responses of patients with unresectable HCC who underwent hepatic arterial infusion chemotherapy

Figure 2. The Kaplan-Meier curves of PFS of patients with unresectable HCC with and without PVTT. The median PFS is 5.8 (95% CI, 4.5–7.1) months in the HCC-without-PVTT group and 5.5 (95% CI, 4.3–6.7) months in the HCC-with-PVTT group (P = 0.897). CI, confidence interval; HCC, hepatocellular carcinoma; PFS, progression-free survival; PVTT, portal vein tumour thrombosis.
HAIC, the ORRs of the intention-to-treat population in the advanced HCC and unresectable large HCC were 29.4% and 46%, respectively [19, 25], which were similar to our findings.

In the IMbrave150 trial, atezolizumab plus bevacizumab was administered to patients with unresectable HCC [26]. The results showed better OS and PFS in recipients of sorafenib,
with an ORR of 27%. In this study of HAIC, we observed ORRs of 44.2% and 38.8% in patients with BCLC stage B and C HCC, respectively. HAIC significantly reduced patients’ costs, potentially improving treatment accessibility.

This study has some limitations. First, this was a retrospective, single-centre study; thus, selection bias may have influenced our results. Second, the number of included patients was small, especially in the HCC-without-PVTT group, and the median follow-up durations were only 9.0 and 9.4 months for the HCC-without-PVTT and HCC-with-PVTT groups, respectively. Adequately powered, prospective, multi-centre studies are needed to verify our findings.

Conclusion
HAI-OR may be efficacious for patients with unresectable HCC—both with and without PVTT.

Authors’ Contributions
S.C. and C.C. designed the study; S.C., W.Y., K.Z., W.L., and X.W. collected and analysed the data; S.C., W.Y., K.Z., W.L., and X.W. performed the statistical analysis; C.C. reviewed the results; S.C. drafted the manuscript; C.C. reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest
None declared.

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