

# A novel chemotherapy strategy for advanced hepatocellular carcinoma: a multicenter retrospective study

Juxian Sun<sup>1</sup>, Chang Liu<sup>2</sup>, Jie Shi<sup>3</sup>, Nanya Wang<sup>4</sup>, Dafeng Jiang<sup>5</sup>, Feifei Mao<sup>1,6</sup>, Jingwen Gu<sup>1</sup>, Liping Zhou<sup>1</sup>, Li Shen<sup>3</sup>, Wan Yee Lau<sup>1,7</sup>, Shuqun Cheng<sup>1</sup>

<sup>1</sup>Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai 200433, China;

<sup>2</sup>Department of Integrative Oncology, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai 200433, China;

<sup>3</sup>Department of Outpatient Department, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai 200433, China;

<sup>4</sup>Department of Oncology, First Hospital of Jilin University, Changchun, Jilin 130000, China;

<sup>5</sup>Department of Oncology Zhejiang Sian International Hospital, Jiaxing, Zhejiang 314000, China;

<sup>6</sup>Tongji University Cancer Center, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200040, China;

<sup>7</sup>Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR 999077, China.

## Abstract

**Background:** Chemotherapy is a common treatment for advanced hepatocellular carcinoma, but the effect is not satisfactory. The study aimed to retrospectively evaluate the effects of adding all-trans-retinoic acid (ATRA) to infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) for advanced hepatocellular carcinoma (HCC).

**Methods:** We extracted the data of patients with advanced HCC who underwent systemic chemotherapy using FOLFOX4 or ATRA plus FOLFOX4 at the Eastern Hepatobiliary Surgery Hospital, First Hospital of Jilin University, and Zhejiang Sian International Hospital and retrospectively compared for overall survival. The Cox proportional hazards model was used to calculate the hazard ratios for overall survival and disease progression after controlling for age, sex, and disease stage.

**Results:** From July 2013 to July 2018, 111 patients with HCC were included in this study. The median survival duration was 14.8 months in the ATRA plus FOLFOX4 group and 8.2 months in the FOLFOX4 only group ( $P < 0.001$ ). The ATRA plus FOLFOX4 group had a significantly longer median time to progression compared with the FOLFOX4 group (3.6 months *vs.* 1.8 months,  $P < 0.001$ ). Hazard ratios for overall survival and disease progression were 0.465 (95% confidence interval: 0.298–0.726;  $P = 0.001$ ) and 0.474 (0.314–0.717;  $P < 0.001$ ) after adjusting for potential confounders, respectively.

**Conclusion:** ATRA plus FOLFOX4 significantly improves the overall survival and time to disease progression in patients with advanced HCC.

**Keywords:** Hepatocellular carcinoma; ATRA plus FOLFOX4; Overall survival; All-trans-retinoic acid; Fluorouracil; Leucovorin; Oxaliplatin

## Introduction

Hepatocellular carcinoma (HCC) remains the sixth most common neoplasm and the third most common cause of cancer-related deaths worldwide.<sup>[1,2]</sup> Current estimates show that nearly 700,000 new cases are diagnosed annually; however, among them, only 15% of patients received appropriate curative therapies, such as partial hepatectomy, liver transplantation, and thermal ablation.<sup>[3]</sup> Moreover, numerous patients are not suitable for curative therapies with a poor prognosis, such as patients with distant metastasis or portal vein tumor thrombus. Additionally, systemic chemotherapy has been widely regarded as ineffective for patients with HCC, especially

for advanced-stage HCC.<sup>[4-6]</sup> However, a recent multicenter, randomized, phase III study, namely Evaluating Avelumab in Combination With Cetuximab in Head and Neck Cancer (EACH), comparing 184 patients with advanced HCC treated with oxaliplatin plus fluorouracil/leucovorin (FOLFOX4) and 184 patients treated with doxorubicin found that FOLFOX4 significantly prolonged overall survival, progression-free survival, and response rate (RR) among selected patients with advanced HCC,<sup>[7]</sup> although the partial response (PR) rate was only 8.15% and no complete response (CR) was observed. The results of the aforementioned study suggest that several chemotherapies

Juxian Sun, Chang Liu and Jie Shi contributed equally to this work.

**Correspondence to:** Prof. Shuqun Cheng, Department of Hepatic Surgery VI, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Changhai Rd 168, Yangpu district, Shanghai 200433, China  
E-Mail: chengshuqun@aliyun.com

Copyright © 2022 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2022;135(19)

Received: 30-12-2021; Online: 23-09-2022 Edited by: Yanjie Yin and Xiuyuan Hao

Access this article online	
Quick Response Code:	Website: www.cmj.org
	DOI: 10.1097/CM9.0000000000001952

might be effective for advanced HCC and warrant further evaluation.

Although all-trans-retinoic acid (ATRA) has been regarded as the first effective targeted therapy for acute promyelocytic leukemia, its effects on solid cancers have rarely been reported.<sup>[8]</sup> Reports have shown that compared with ATRA alone, ATRA followed by intensive chemotherapy provided a significant improvement in the event-free survival among patients with acute promyelocytic leukemia. Our previous studies have also shown that ATRA could significantly improve the treatment effect of cisplatin in patients with HCC.<sup>[9,10]</sup> This could be partially attributed to the effects of ATRA-induced differentiation of HCC tumor-initiating cells (TICs) with a resultant decrease in the chemoresistant subpopulation. To evaluate the effects of adding ATRA to FOLFOX4 on advanced HCC, we, therefore, conducted a multicenter retrospective study including 111 patients with advanced HCC.

## Methods

### Ethical approval

This study was approved by the Ethics Committee of Eastern Hepatobiliary Surgery Hospital (EHBHKY2020-01-013). Informed consent was obtained from all patients prior to treatment, and for their data to be used in research purposes.

### Patients

Patients with histologically, cytologically, or clinically diagnosed unresectable HCC treated at the Eastern Hepatobiliary Surgery Hospital (Shanghai, China), the First Hospital of Jilin University (Changchun, China), and the Zhejiang Sian International Hospital (Jiaying, China) from July 2013 to June 2018 were enrolled into this study. The inclusion criteria were as follows: age >18 years; advanced HCC with or without extrahepatic metastases (BCLC [Barcelona Clinic Liver Cancer] stage: C); with the liver functional status of Child-Pugh Grade A or B but without a history of encephalopathy or upper gastrointestinal bleeding; white blood cell count  $\geq 4.0 \times 10^9/L$ , hemoglobin  $\geq 90$  g/L, and platelet count  $\geq 100 \times 10^9/L$ ; and life expectancy of  $\geq 12$  weeks. The exclusion criteria were patients with hepatic encephalopathy; hemorrhagic disorders or active bleeding; sepsis; New York Heart Association classification for congestive heart failure >2, active coronary artery disease or cardiac ischemia, uncontrolled cardiac arrhythmias even with anti-arrhythmic therapy; and patients who underwent radiotherapy, trans-arterial chemoembolization, radiofrequency ablation, microwave ablation, and hormonal therapy within 4 weeks.

### Systemic chemotherapy

In the ATRA plus FOLFOX4 (ATFOX) group, the treatment regimen consisted of ATRA 20 mg orally 3 times/day for 3 days before the initiation of FOLFOX4. ATRA was discontinued at the end of FOLFOX4. FOLFOX4 therapy included oxaliplatin 85 mg/m<sup>2</sup> administered intravenously (IV) on the first day,

leucovorin 200 mg/m<sup>2</sup> IV from 0 to 4 h on the first day, and 5 fluorouracil

(5-FU) 400 mg/m<sup>2</sup> IV bolus at the 4th hour, followed by 600 mg/m<sup>2</sup> for at least 40 h in the first 2 days, once every 2 weeks. The FOLFOX4 group only provided the FOLFOX4 therapy. The dosage of the medications was calculated in milligrams of each drug per square meter of body surface area as measured (mg/m<sup>2</sup>). The body surface area was reevaluated when changes in body weight were  $\geq 5\%$ .

### Evaluation and follow-up

The liver function of all patients was closely evaluated and monitored during and after chemotherapy and follow-up. Abdominal ultrasound and chest radiography were conducted and liver function parameters, alpha-fetoprotein levels, and Des-Gamma-Carboxy prothrombin levels were measured every 4 weeks. For patients with concurrent lung metastasis, chest computed tomography (CT) was performed once every 3 months. For patients with intraperitoneal or lymphatic metastasis, abdominal CT, or magnetic resonance imaging (MRI) was performed once every 3 months. Upon disease progression or the occurrence of liver failure or massive ascites, standard supportive care was provided.

Overall survival was defined as the duration from the chemotherapy start date to the date of death. The time to progression was defined as the duration from the chemotherapy start date to the date of tumor progression. RR was evaluated and determined by an independent radiologist according to the modified Response Evaluation Criteria in Solid Tumors (RECIST).

Safety assessments, including vital signs, physical examination, electrocardiogram, echo, clinical laboratory tests, and special medical imaging (chest radiography, CT, MRI, and bone scan), were closely evaluated and recorded. All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0).

### Statistical analyses

We calculated the medians (range) and compared them by using the independent *t* test for continuous variables in two groups. The chi-squared tests were used to compare differences in categorical variables between two groups. The overall survival in the two groups was determined using Kaplan-Meier curves and compared using the log-rank test. All statistical analyses were performed using SPSS (version 16.0; Chicago, IL, USA), with a *P* value < 0.05 indicating statistically significant.

## Results

### Patient characteristics

Among the 111 patients with advanced HCC, 83.8% (93/111) were male. The mean age in the FOLFOX and ATRA plus FOLFOX groups was 50.2 ( $\pm 10.3$ ) years and 52.9 ( $\pm 18.7$ ) years, respectively [Table 1]. Moreover, 85.6% (95/111) of the patients (87.0% [47/54] from the

**Table 1: The clinicopathological features of advanced hepatocellular carcinoma patients (n = 111).**

Variables	FOLFOX (n = 54)	ATRA +FOLFOX (n = 57)	P value
Age (years)	50.2 ± 10.3	52.9 ± 18.7	0.280
Sex			0.522
Male	44 (81.5)	49 (86.0)	
Female	10 (18.5)	8 (14.0)	
HBsAg			0.672
Negative	7 (13.0)	9 (15.8)	
Positive	47 (87.0)	48 (84.2)	
α-Fetoprotein			0.009
<400 μg/L	18 (33.3)	33 (57.9)	
≥400 μg/L	36 (66.7)	24 (42.1)	
ALT			0.313
<44 U/L	34 (63.0)	41 (71.9)	
>44 U/L	20 (37.0)	16 (28.1)	
ALP			0.165
≥35 U/L	54 (100.0)	55 (96.5)	
<35 U/L	0	2 (3.5)	
TB			0.081
>35 μmol/L	5 (9.3)	1 (1.8)	
<35 μmol/L	49 (90.7)	56 (98.2)	
PLT			0.941
≥100 × 10 <sup>9</sup> /L	12 (22.2)	13 (22.8)	
<100 × 10 <sup>9</sup> /L	42 (77.8)	44 (77.2)	
WBC			0.545
≥4000 × 10 <sup>9</sup> /L	34 (63.0)	39 (68.4)	
<4000 × 10 <sup>9</sup> /L	20 (37.0)	18 (31.6)	
BCLC			0.702
B	14 (25.9)	13 (22.8)	
C	40 (74.1)	44 (77.2)	
Okuda			0.331
I	37 (68.5)	34 (59.6)	
II	17 (31.5)	23 (40.4)	
PVTT			0.188
Yes	14 (25.9)	9 (15.8)	

Data are presented as mean±standard deviation or n (%). ATRA: All-trans-retinoic acid; PVTT: Portal vein tumor thrombosis; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; PLT: Platelet; TB: Total bilirubin; WBC: White blood cell.

FOLFOX group and 84.2% [48/57] from the ATRA plus FOLFOX group) were positive for hepatitis B surface antigen. Most of the characteristics in the two therapeutic groups were similar before chemotherapy (all P values >0.05). Only the percentage of α-fetoprotein >400 ng/mL differed between the groups, with the FOLFOX group (66.7% [36/54]) showing significantly higher percentages compared with the ATRA plus FOLFOX group (42.1% [24/57]) (P = 0.009). All patients had a Child–Pugh A liver function and Eastern Cooperative Oncology Group performance status of 0 or 1. Most patients (n = 85, 76.6%) were classified as BCLC stage C. The median chemotherapy cycle was 3.7 (range: 1–16 cycles). Overall, 57 and 54 patients received ATRA plus FOLFOX4 and FOLFOX4 only, respectively. The median follow-up duration was 12 months (range: 5–55 months). At the end of this study, 20 and 6 patients in the ATRA plus FOLFOX4 and FOLFOX4 groups survived, respectively.

**Survival**

The median overall survival was 8.2 and 14.9 months in the FOLFOX4 and ATRA + FOLFOX4 groups, respectively (P < 0.001). The corresponding 6-month, 1-year, and 2-year survival rates were 50.0%, 31.5%, and 7.4% in the FOLFOX4 group and 93.0%, 56.1%, and 14.0% in the ATRA + FOLFOX4 group, respectively [Figure 1]. After adjusting for age, sex, and stage of diseases, the HR for overall survival was 0.465 (95% confidence interval [CI]: 0.298–0.726; P = 0.001). The median time to progression was 1.8 and 3.6 months in the FOLFOX4 and ATRA + FOLFOX4 groups, respectively (P < 0.001). The corresponding 6-month, 1-year, and 2-year disease-free survival rates were 18.5%, 9.3%, and 0.0% in the FOLFOX4 group and 35.1%, 24.6%, and 5.3% in the ATRA + FOLFOX4 group, respectively [Figure 2]. After adjusting for age, sex, and stage of diseases, the HR of disease-free survival was 0.474 (95% CI: 0.314–0.717; P < 0.001).

Univariate analysis showed ATRA (P = 0.004), Okuda stage (P = 0.017), portal vein tumor thrombosis (PVTT) (P = 0.039), extrahepatic lesions (P = 0.002), and BCLC stage (P = 0.037) were independent prognostic factors of OS, whereas multivariate analysis showed only ATRA (P = 0.005) and extrahepatic lesions (P = 0.017) were independent prognostic factors of OS.

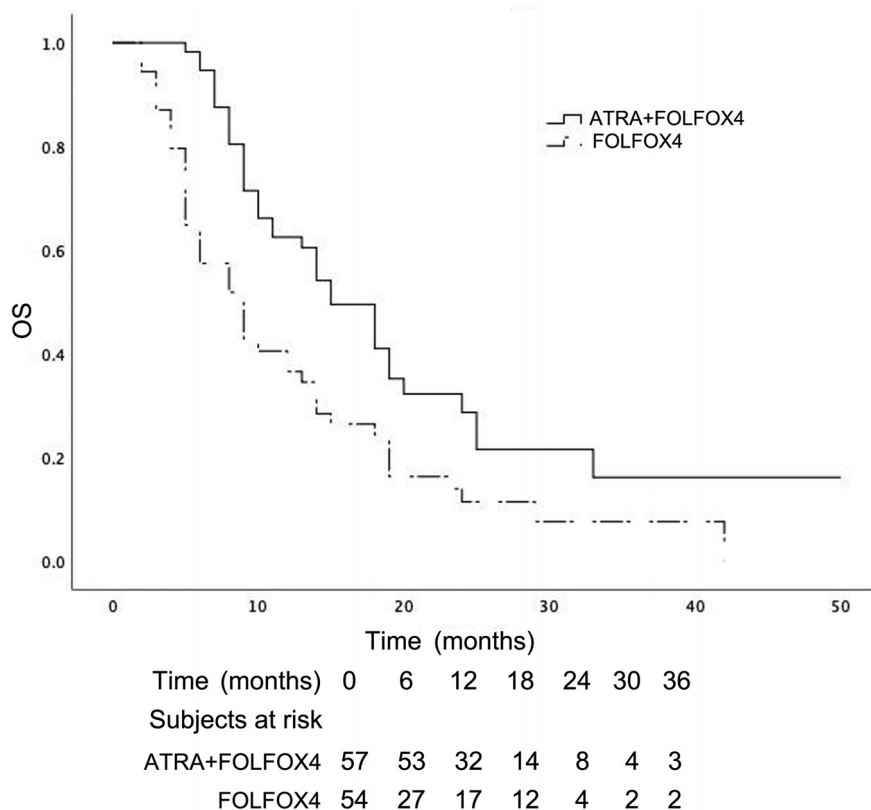
The ATRA + FOLFOX4 group had a RR of 22.8% (13/57), including four patients with complete remission. Meanwhile, the FOLFOX4 group had a RR of 9.3% (5/54), with no patient demonstrating a CR [Table 2]. The disease control rate (DCR) was 29.6% (16/54) and 52.6% (30/57) in the FOLFOX4 and ATRA + FOLFOX4 groups, respectively.

**Survival analysis in the patient subgroups**

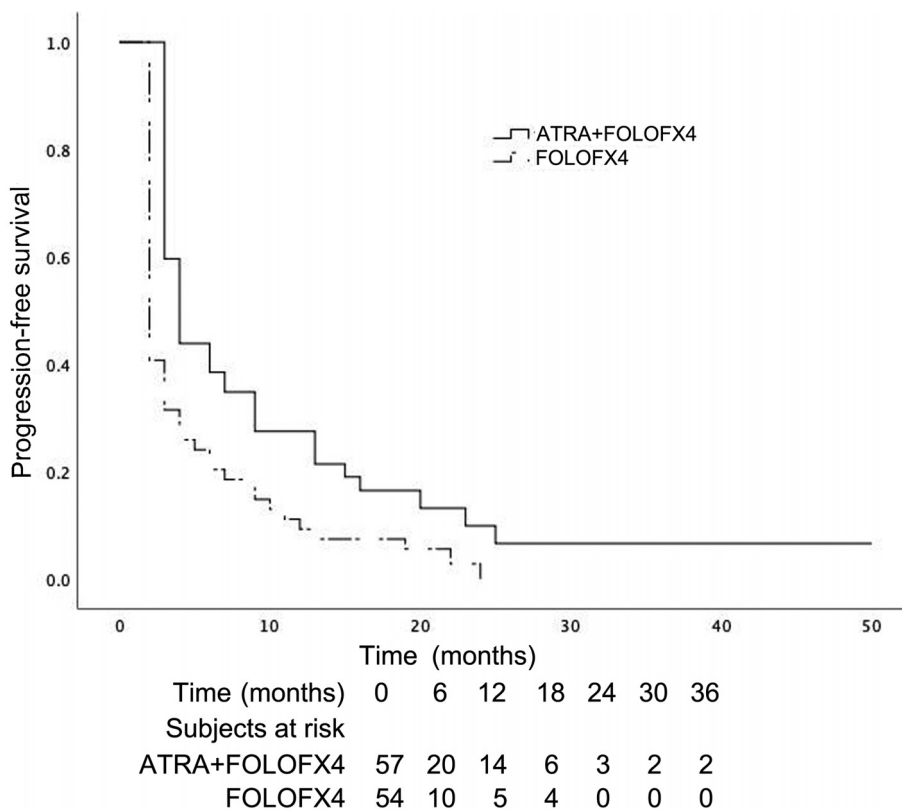
Among patients with hepatic tumor alone, no significant difference in OS was observed between both groups (9.6 months vs. 11.6 months, respectively; P > 0.05). However, among patients with both hepatic tumor and extrahepatic lesions, the ATRA + FOLFOX4 group had a significantly better OS compared with the FOLFOX4 group (14.3 months vs. 9.6 months, respectively; P = 0.02).

**Adverse events**

Table 3 summarizes Grade 3 adverse events. Fatigue, anorexia, nausea, and leukocytopenia were the most common acute adverse events, although most were Grade 1 or 2. NCI CTCAE Grade 1 or 2 headaches occurred in approximately 10% of patients in the ATRA + FOLFOX4 group, with no headaches having been observed in the FOLFOX4 group. However, non-steroidal anti-inflammatory drugs were effective in controlling and alleviating the pain. For gastrointestinal complications, four patients in each group experienced nausea with NCI CTCAE Grade 3, whereas one patient in each group had liver function damage with NCI CTCAE Grade 3. No treatment-related deaths were observed in this study.



**Figure 1:** Kaplan–Meier curve of overall survival In the ATRA+ FOLFOX4 and FOLFOX4 groups. ATRA: All-trans-retinoic acid; FOLFOX4: Infusional fluorouracil, leucovorin, and oxalplatin; OS: Overall survival.



**Figure 2:** Kaplan–Meier curve of progression-free survival In the ATRA + FOLOFX4 and FOLOFX4 groups. ATRA: All-trans-retinoic acid; FOLFOX4: Infusional fluorouracil, leucovorin, and oxalplatin.

**Table 2: Disease response of advanced hepatocellular carcinoma patients (n = 111).**

Parameter	ATRA + FOLFOX (n = 57)	FOLFOX4 (n = 54)	P value
RR*	13 (22.8)	5 (9.3)	0.053
DCR†	30 (52.6)	16 (29.6)	0.014
CR	4 (7.0)	0	0.047
PD	27 (47.4)	38 (70.4)	0.014

\* Defined as CR plus PR. Data are presented as n (%). † Defined as CR plus PR plus SD. ATRA: All-trans-retinoic acid; CR: Complete response; DCR: Disease control rate; FOLFOX4: Infusional fluorouracil, leucovorin, and oxaliplatin; PR: Partial response; PD: Progressive disease; RR: Response rate.

**Table 3: Adverse events of patients with advanced hepatocellular carcinoma who underwent chemotherapy.**

Adverse event	No. of patients with CTCAE Grade 3/4 (n)	
	FOLFOX4	ATRA + FOLFOX
Headache	–	–
Fatigue	2	3
Nausea	4	4
Diarrhea	–	–
Thrombocytopenia	–	–
Leukocytopenia	11	11
ALT increase	1	1
Bilirubin increase	1	1
ALP increase	0	1
Hypoalbuminemia	–	–

ATRA: All-trans-retinoic acid; CTCAE: Common Terminology Criteria for Adverse Events; FOLFOX4: Infusional fluorouracil, leucovorin, and oxaliplatin; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

**Discussion**

This study retrospectively compared the efficacy and safety between 57 patients receiving ATRA + FOLFOX4 with 54 patients receiving FOLFOX4. Overall, our finding showed that combined ATRA and FOLFOX4 therapy promoted significantly longer overall and progression-free survival in patients with advanced HCC compared with FOLFOX4 therapy alone. Moreover, the RR, DCR, and completion rates were significantly improved. The combined treatment did not significantly increase the rates of severe adverse effects.

Reports have shown that 85% of patients with HCC are diagnosed with advanced-stage disease. Despite being diagnosed at an earlier stage and undergoing “curative” liver resection, a large proportion of patients with HCC may still experience a recurrence in the future.<sup>[3]</sup> Currently, firstline therapy for advanced HCC comprises sorafenib and lenvatinib, whereas second-line treatments comprise regorafenib, cabozantinib, and ramucirumab. All of the aforementioned drugs have been demonstrated to improve survival outcomes of patients with HCC. However, the median overall survival of patients with HCC remains <1 year, with RRs of only 2% to 3%<sup>[11]</sup> and CR being rare.<sup>[12]</sup>

With constant progress in systemic chemotherapy, recent evidence from clinical trials has shown that chemotherapy

might be beneficial for the treatment of patients with HCC.<sup>[13]</sup> In the EACH study, the PR rate of patients with HCC was only 8.15%, with no patients exhibiting a CR. Given the poor outcomes of current treatment and lack of effective therapeutic options for patients with HCC, portal vein tumor thrombus, or distant metastasis, new treatments, and efficient options are urgently needed. Therefore, the current study explored and evaluated the combined ATRA and FOLFOX4 therapy, subsequently finding that such a combined therapy promoted longer overall and progression-free survival compared with FOLFOX4 alone in patients with advanced HCC. Among the included patients, >70% had BCLC stage C HCC. However, the BCLC stage was not significantly associated with overall survival in our multivariable Cox model. This might be attributed to the small and unbalanced sample size of patients in both stages. Moreover, four patients with concurrent metastatic lung lesions and one patient with abdominal peritoneal metastatic lesions in the combined treatment group showed a CR at the end of the study. Therefore, combined ATRA and FOLFOX4 therapy might be an effective therapeutic option for patients with advanced HCC. However, further well-designed randomized controlled trials are needed to confirm our findings. Additionally, the mechanism of synergy should be further studied to improve the curative effect and reduce the incidence of side effects.

Drug resistance still remains the largest obstacle hindering improvements in survival duration and rates in patients with HCC. Recently, accumulating evidence has suggested that TICs exhibit greater resistance to conventional chemotherapy compared with non-TICs. Consistently, a study evaluating doxorubicin and 5-FU-resistant hepatic cancer cells demonstrated that doxorubicin and 5-FU-resistant hepatic cancer cells exhibited stem-like properties.<sup>[14]</sup> Stem cell phenotype CD133 + HCC cells had greater chemoresistance to doxorubicin and 5-FU compared with CD133- cells.<sup>[15]</sup> Taken together, the aforementioned findings suggest that specific therapies targeting TICs might enhance the effects of chemotherapy.

ATRA, the most thoroughly studied differentiation inducer, has been known to strongly induce the differentiation of different types of tumor cells, including stem cells. Our previous studies<sup>[9,10]</sup> showed that ATRA could induce the differentiation of HCC TICs via the TSC2/AKT pathway and that combined treatment with ATRA and cisplatin could improve the therapeutic effect by eliminating TICs via ATRA-induced differentiation *in vivo* and *in vitro*. Moreover, the current study provided clinical evidence to support the improved therapeutic effect of the combined treatment.

Combining ATRA with FOLFOX4 was more effective among patients with HCC who had extrahepatic metastases rather than hepatic lesions alone or PVTT. This result suggested that systemic chemotherapy might not be suitable for the treatment of patients with hepatic lesions alone. Among patients with only hepatic tumors, no significant difference in overall survival and time to progression was observed between both groups. However, ATRA/FOLFOX promoted significantly better survival

outcomes in patients with concurrent hepatic and extrahepatic lesions.

The limitation of this study is its retrospective design, small sample size, non-randomized comparison, and failure to determine causality.<sup>[16]</sup> Additionally, some residual confounders were not included in this study given the retrospective study design, with a considerable portion of information being unavailable. Therefore, a well-designed, randomized comparative trial with a large sample size is needed to confirm our findings.

To conclude, combined ATRA and FOLFOX4 therapy was more effective compared with FOLFOX4 alone in the treatment of patients with advanced HCC. The combined treatment, which promoted less severe adverse effects, might be considered for those patients with advanced HCC, especially those with advanced disease stages.

### Acknowledgements

The authors would like to acknowledge Prof. Lau Wan Yee for providing writing support.

### Funding

This work is supported by the National Natural Science Foundation of China (No.82073293); Clinical Science and Technology Innovation Project of Shanghai Shenkang Hospital Development Center (Joint Project of Emerging Frontier Technology) (SHDC12018116); the Key Project of Natural Science Foundation of China (No: 81730097).

### References

- Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018;391:1301–1314. doi: 10.1016/S0140-6736(18)30010-2.
- Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, *et al.* Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115–132. doi: 10.3322/caac.21338.
- Roxburgh P, Evans TRJ. Systemic therapy of hepatocellular carcinoma: are we making progress? *Adv Ther* 2008;25:1089–1104. doi: 10.1007/s12325-008-0113-z.
- Küley-Bagheri Y, Kreuzer KA, Monsef I, Lübbert M, Skoetz N. Effects of all-trans retinoic acid (ATRA) in addition to chemotherapy for adults with acute myeloid leukaemia (AML) (non-acute promyelocytic leukaemia (non-APL)). *Cochrane Database Syst Rev* 2018;8:11960–12024. doi: 10.1002/14651858.CD011960.pub2.
- Gish RG, Porta C, Lazar L, Ruff P, Feld R, Croitoru A, *et al.* Phase III randomized controlled trial comparing the survival of patients with unresectable hepatocellular carcinoma treated with nolatrexed or doxorubicin. *J Clin Oncol* 2007;25:3069–3075. doi: 10.1200/JCO.2006.08.4046.
- Yeo W, Mok TS, Zee B, Leung TWT, Lai PBS, Lau WY, *et al.* A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst* 2005;97:1532–1538. doi: 10.1093/jnci/dji315.
- Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, *et al.* Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. *J Clin Oncol* 2013;31:3501–3508. doi: 10.1200/JCO.2012.44.5643.
- Wei S, Kozono S, Kats L, Nechama M, Li W, Guarnerio J, *et al.* Active Pin1 is a key target of all-trans retinoic acid in acute promyelocytic leukemia and breast cancer. *Nat Med* 2015;21:457–466. doi: 10.1038/nm.3839.
- Zhang Y, Guan DX, Shi J, Gao H, Li JJ, Zhao JS, *et al.* All-trans retinoic acid potentiates the chemotherapeutic effect of cisplatin by inducing differentiation of tumor initiating cells in liver cancer. *J Hepatol* 2013;59:1255–1263. doi: 10.1016/j.jhep.2013.07.009.
- Guan DX, Shi J, Zhang Y, Zhao JS, Long LY, Chen TW, *et al.* Sorafenib enriches epithelial cell adhesion molecule-positive tumor initiating cells and exacerbates a subtype of hepatocellular carcinoma through TSC2-AKT cascade. *Hepatology* 2015;62:1791–1803. doi: 10.1002/hep.28117.
- Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al.* Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–390. doi: 10.1056/NEJMoa0708857.
- Shiozawa K, Watanabe M, Ikehara T, Matsukiyo Y, Kogame M, Kanayama M, *et al.* Sustained complete response of hepatocellular carcinoma with portal vein tumor thrombus following discontinuation of sorafenib: a case report. *Oncol Lett* 2014;7:50–52. doi: 10.3892/ol.2013.1664.
- Yang H, Woo HY, Lee SK, Han JW, Jang B, Nam HC, *et al.* A comparative study of sorafenib and metronomic chemotherapy for Barcelona Clinic Liver Cancer-stage C hepatocellular carcinoma with poor liver function. *Clin Mol Hepatol* 2017;23:128–137. doi: 10.3350/cmh.2016.0071.
- Vu NB, Nguyen TT, Tran LC, Do CD, Nguyen BH, Phan NK, *et al.* Doxorubicin and 5-fluorouracil resistant hepatic cancer cells demonstrate stem-like properties. *Cytotechnology* 2013;65:491–503. doi: 10.1007/s10616-012-9511-9.
- Ma S, Lee TK, Zheng BJ, Chan KW, Guan XY. CD133+ HCC cancer stem cells confer chemoresistance by preferential expression of the Akt/PKB survival pathway. *Oncogene* 2008;27:1749–1758. doi: 10.1038/sj.onc.1210811.
- Shi J, Sun J, Liu C, Chai Z, Wang N, Zhang H, *et al.* All-trans-retinoic acid (ATRA) plus oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX) versus FOLFOX alone as palliative chemotherapy in patients with advanced hepatocellular carcinoma and extrahepatic metastasis: study protocol for a randomized controlled trial. *Trials* 2019;20:245–254. doi: 10.1186/s13063-019-3349-9.

**How to cite this article:** Sun J, Liu C, Shi J, Wang N, Jiang D, Mao F, Gu J, Zhou L, Shen L, Lau WY, Cheng S. A novel chemotherapy strategy for advanced hepatocellular carcinoma: a multicenter retrospective study. *Chin Med J* 2022;135:2338–2343. doi: 10.1097/CM9.0000000000002277