World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i28.4552

*World J Gastroenterol* 2013 July 28; 19(28): 4552-4558
ISSN 1007-9327 (print) ISSN 2219-2840 (online)


BRIEF ARTICLE

# Efficacy of capecitabine and oxaliplatin regimen for extrahepatic metastasis of hepatocellular carcinoma following local treatments

Sheng-Li He, Jie Shen, Xian-Jun Sun, Xiao-Juan Zhu, Lu-Ming Liu, Jing-Cheng Dong

Sheng-Li He, Jie Shen, Xian-Jun Sun, Xiao-Juan Zhu, Department of Hepato-Biliary and Pancreatic Oncology, Fudan University Shanghai Cancer Center, Shanghai 200240, China
Lu-Ming Liu, Department of Integrative Oncology, Fudan University Shanghai Cancer Center, Shanghai 200032, China
Jing-Cheng Dong, Department of Integrative Medicine, Huashan Hospital Affiliated to Fudan University, Shanghai 200040, China
Author contributions: Sun XJ, Zhu XJ, Liu LM and Dong JC performed the majority of the study, collected data and followed up the patients; Shen J provided analytical tools and revised the manuscript; He SL designed the study and wrote the manuscript.
Supported by Shanghai Municipal Health Bureau Outstanding Young Clinical Personal Training Project, No. ZYSNXD-YL-YSZK025
Correspondence to: Dr. Sheng-Li He, Department of Hepato-Biliary and Pancreatic Oncology, Fudan University Shanghai Cancer Center, Minhang Branch, Shanghai 200240, China. hlshli@yeah.net
Telephone: +86-21-64629290 Fax: +86-21-64633901
Received: March 21, 2013 Revised: April 25, 2013
Accepted: June 1, 2013
Published online: July 28, 2013

## Abstract

**AIM:** To investigate the efficacy and safety of capecitabine and oxaliplatin (CapeOx) for extrahepatic metastasis after local treatment of hepatocellular carcinoma (HCC).

**METHODS:** Thirty-two patients with extrahepatic metastasis of HCC after local treatment were prospectively enrolled. The CapeOx regimen consisted of capecitabine 1000 mg/m$^2$ taken orally twice daily on days 1-14, and oxaliplatin was administered at a total dose of 100 mg/m$^2$ on day 1. The treatment was repeated every 3 wk until disease progression or unacceptablle toxicity. Efficacy and safety were assessable for all enrolled patients. The primary objective of this study was to assess the overall response rate. The secondary objectives were to evaluate the overall survival (OS), the time to tumor progression (TTP) and the toxicity profile of the combined strategy. TTP and OS were assessed by the Kaplan-Meier method and differences between the curves were analyzed using the log-rank test. The statistical software SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, United States) was used for statistical analysis. All *P* values were 2-tailed, with statistical significance defined by $P \leqslant 0.05$.

**RESULTS:** Thirty-two patients were assessable for efficacy and toxicity. The median follow-up duration was 15 mo (range, 12-20 mo). At the cut-off date of March 31, 2012, 27 patients died due to tumor progression and one patient died of myocardial infarction. Four patients were still alive (three patients with disease progression). OR was 21.9% ($n$ = 7), the stabilization rate was 40.6% ($n$ = 13), and the disease control rate was 62.5%. The responses lasted from 4 to 19 mo (median, 6 mo). Median TTP was 4.2 mo (95%CI: 2.5-7.4), and the median OS time was 9.2 mo (95%CI: 6.5-17.8). The 1-year survival rate was 43.6% (95%CI: 29.0-66.0). In a multivariate analysis, OS was significantly longer in patients with a Child-Pugh class A compared with class B patients ($P$ = 0.014), with a median OS of 10.1 mo *vs* 5.4 mo, and there were trends towards longer OS ($P$ = 0.065) in patients without portal vein tumor thrombosis. There were no significant effects of age, gender, performance status, cirrhosis, metastatic sites, and level of alpha fetoprotein (AFP) or hepatitis B virus-DNA on OS. Among the 22 patients with elevated AFP levels at baseline ($\geqslant$ 400 ng/mL), the level fell by more than 50% during treatment in 6 patients (27.3%). The most frequent treatment-related grade 3 to 4 toxicities included leucopenia/neutropenia, transient elevation of aminotransferases, hand-foot syndrome and fatigue.

**CONCLUSION:** CapeOx showed modest anti-tumor activity in metastatic HCC. However, the manageable

toxicity profile and the encouraging disease control rate deserve further study for these patients.



**Key words:** Hepatocellular carcinoma; Extrahepatic metastasis; Capecitabine; Oxaliplatin; Local treatments

**Core tip:** Distant metastases are still obstacles in improvement of outcome in hepatocellular carcinoma (HCC) patients after local treatment. Although, sorafenib is used as a standard systemic treatment for those patients, it is not suitable for patients with intermediate HCC who were not eligible to or failed in the locoregional therapy. This study reports the capecitabine and oxaliplatin regimen for extrahepatic metastasis after local treatment of HCC. The objective response rate was 21.9%, and 40.6% of patients had stable disease, and the median overall survival and the time to tumor progression were 4.2 and 9.2 mo, respectively. Furthermore, the result of this study showed that toxicity profile was tolerated well.

He SL, Shen J, Sun XJ, Zhu XJ, Liu LM, Dong JC. Efficacy of capecitabine and oxaliplatin regimen for extrahepatic metastasis of hepatocellular carcinoma following local treatments. *World J Gastroenterol* 2013; 19(28): 4552-4558 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i28/4552.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i28.4552

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide, with the incidence on the rise[1]. The overall 5-year survival rate for all HCC patients has remained no more than 5%[2]. Surgical resection, local ablation, transarterial chemoembolization (TACE) and liver transplantation are the mainstay of treatment of localized HCC, but local recurrence and distant metastasis are still obstacles in the further improvement of outcome in HCC patients after local treatments. Sorafenib, a small molecule multikinase inhibitor, was the first systemic agent used to prolong survival of patients with advanced HCC, as demonstrated in two phase Ⅲ trials and it is now the reference standard for systemic treatment of these patients[3,4]. However, its efficacy and safety have not been demonstrated in patients with poor liver function (Child-Pugh class B)[5]. Moreover, patients with extrahepatic metastasis had a greater risk of death than those with intrahepatic disease treated by sorafenib[6]. Systemic treatment with oral targeted therapy may be lifelong and expensive. In addition, sorafenib is not covered in the scope of health insurance for advanced HCC in China. Therefore, systemic treatment options remain to be defined in patients with extrahepatic metastasis of HCC after local treatments.

Capecitabine is a rationally designed, orally administered, tumor-selective fluoropyrimidine that mimics continuous infusion of 5-fluorouracil (5-FU). Capecitabine was found to be safe in patients with cirrhosis and provided an 11% response rate (RR) including radiologically confirmed complete response (CR) in one patient[7]. Oxaliplatin has consistently shown preclinical and clinical anti-tumor activity against gastrointestinal cancers. In metastatic colorectal cancer, oxaliplatin in combination with 5-FU resulted in response rates of 20%-50% and median progression-free survival (PFS) of approximately 7.5-9.0 mo in randomized trials[8]. A phase Ⅲ study of 5-FU/oxaliplatin conducted in Asian patients suffering from inoperable or metastatic HCC showed the feasibility and demonstrated its superior efficacy compared with doxorubicin[9].

Response evaluation for intrahepatic lesions in patients with advanced HCC is difficult because of variability of both tumor growth pattern and results of previous local treatments including TACE, ablation or radiation therapy[10]. Therefore, this study selected advanced HCC patients with at least one measurable extrahepatic metastatic lesion. The regimen of capecitabine and oxaliplatin (CapeOx) for patients with extrahepatic metastatic HCC was based on (1) the synergy of these two drugs in patients with advanced or metastatic solid tumors[11]; (2) the regimen of oxaliplatin and 5-FU with a manageable toxicity profile in cirrhotic Child-Pugh class A-B or liver transplanted patients[12]; (3) the clinical activity and favorable toxicity profile of capecitabine alone and in combination with oxaliplatin in advanced or metastatic colorectal cancer[13,14]; (4) no dose adjustment required for capecitabine and oxaliplatin due to hepatic dysfunction[15]; and (5) the feasibility and efficacy of CapeOx alone or in combination with antiretroviral therapy in patients with human immunodeficiency virus- (and hepatitis C virus-co-) infection and HCC[16]. This study aims to evaluate the efficacy and safety of CapeOx regimen in patients with extrahepatic metastasis following local treatment.

## MATERIALS AND METHODS

### Patients

From March 2009 to March 2012, we enrolled 32 patients with extrahepatic metastasis. Eligibility criteria included the following: (1) initially received surgery, thermal ablation, TACE or TACE combined with radiotherapy; (2) at least one measurable extrahepatic lesion; (3) no previous systemic treatment; (4) World Health Organization (WHO) performance status (PS) 0-2; (5) Child-Pugh class of A or B; and (6) age between 18-70 years and adequate bone marrow, renal and hepatic function (absolute neutrophil count $\geqslant 1.5 \times 10^9$/L and platelet count $\geqslant 80 \times 10^9$/L; serum creatinine $\leqslant$ 1.5 mg/dL; aspartate aminotransferase and alanine aminotransferase $\leqslant 2.5 \times$ upper limits of normal; total bilirubin $\leqslant 1.5 \times$ upper limits of normal). Study entry required a complete medical history, physical examination, complete blood cell with a differential count, biochemistry panel, and a coagulation panel

and serum alpha-fetoprotein (AFP), chest or abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI). Main exclusion criteria were Child-Pugh class C, previous systemic treatment, central nervous system metastases, severe cardiac and/or respiratory failure, concurrent malignancy, and baseline sensitive peripheral neuropathy; pregnant or lactating females. This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The study was approved by the local ethics committee. Informed consent was obtained from all participants.

Before registration, complete blood cell and platelet counts were examined weekly, and physical examination, biology [serum alpha-fetoprotein (AFP), transaminases, alkaline phosphatases, bilirubin, lactate dehydrogenase, γ-glutamyltransferase, albumin, prothrombin time, and creatinine], and safety assessments were performed before each cycle of chemotherapy. Analysis of AFP level and tumor assessment by CT scan or MRI were undertaken every two cycles. Objective response (OR) was confirmed by a second evaluation 4 wk later. Objective and discordant responses were reviewed by an independent radiologist. Treatment was discontinued because of either disease progression and unacceptable toxicity, or patient's refusal. Other treatments were proposed in the event of disease progression.

### Treatment protocol

CapeOx regimen was administered in a 3-wk cycle. In each cycle, oxaliplatin (ELOXATIN®, Sanofi-Aventis, Hangzhou, China) was administered at a total dose of 100 mg/m$^2$ as a 2-h *iv* infusion on day 1, and capecitabine (XELODA®, Shanghai Roche Shanghai, China) 1000 mg/m$^2$ was taken orally twice daily (total daily dose 2000 mg/m$^2$) on days 1-14. Hepatitis B surface antigen positive patients were treated with lamivudine (HEPTODIN®, GlaxoSmithKline, Suzhou, China) 100 mg/d before the first CapeOx cycle to prevent severe hepatitis during treatment. All patients with bone metastases received bisphosphonates treatment once a month. Depending on the severity of side effects, chemotherapy was paused or the dose was reduced. A 20% dose reduction was required based on predefined criteria. Briefly, capecitabine dose was reduced by 20% due to recurrence of grade 3 or 4 diarrhea or hand/foot syndrome. Oxaliplatin dose was reduced by 20% in case of grade 1 or 2 peripheral neuropathy, whereas in case of grade 3 or 4 neuropathy (defined as permanent functioning discomfort), oxaliplatin was discontinued and capecitabine was administered alone as initially scheduled. Patients were considered assessable for toxicity if they had received a minimum of one cycle of treatment.

### Assessment of responses

Baseline evaluation included physical examination, assessment of medical history, evaluation of performance status, and blood counts. During treatment, patients were evaluated before each cycle of therapy with the above parameters. Response was assessed after every two cycles of chemotherapy by CT scan or MRI using the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) criteria[17]. CR was defined as the disappearance of all target and non-target lesions compared to baseline. Partial response (PR) was defined as at least a 30% decrease in the longest diameters of all target lesions, taking as a reference the baseline sum of the diameters with no new lesions appearing. Patients were considered to have progressive disease (PD) if any new lesions appeared, if the tumor size increased by at least 20% in the diameters of the target lesions, taking as reference the smallest sum on study, or if there was unequivocal progression of existing non-target lesions. A patient who did not meet the definition of CR, PR or PD was classified as having stable disease. The percentage of patients who had the best responses (other than PD) according to the RECIST 1.1 criteria, and had those responses maintained for at least 28 d after the first radiologic evaluation, was defined as the disease control rate (DCR). AFP and hepatitis B virus (HBV)-DNA levels were determined every 2 mo. Body weight, PS, and symptoms were recorded before each cycle. Toxic effects of chemotherapy were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0. This specific scale was used to assess oxaliplatin neurotoxicity[18].

### Statistical analysis

The primary objective of this study was to assess the overall response rate. The secondary objectives were to evaluate the overall survival (OS), the time to tumor progression (TTP) and the toxicity profile of the combined strategy. TTP was the interval from the starting date of therapy to the date of progression; OS was defined as the time interval between the first cycle of chemotherapy and death due to any cause or the last clinical follow-up. TTP and OS were assessed by the Kaplan-Meier method and differences between the curves were analyzed using the log-rank test. For the statistical analysis, the statistical software SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, United States) was used. All $P$ values were 2-tailed, with statistical significance defined by $P \leqslant 0.05$.

## RESULTS

Thirty-two patients (21 men and 11 women) were enrolled between March 2009 and March 2012. Median age of the patients was 59 years (range 19-70 years). Chronic HBV infection was the most common etiology of underlying liver disease (23 patients, 71.9%). Two patients (6.3%) had a history of alcohol abuse. Twenty-two (68.8%) patients belonged to Child-Pugh class A and 10 (31.2%) to Child-Pugh class B. Cirrhosis was present in 12 patients (37.5%), and 22 patients (68.8%) had serum AFP (≥ 400 ng/mL). Four patients received curative HCC resection and 19 patients were treated with TACE, 4 patients were treated by TACE combined with radiotherapy after diagnosis. Five patients underwent ablation of HCC. Patients' other baseline characteristics are summarized in Table 1.

**Table 1 Patient and tumor characteristics at baseline ($n$ = 32)**

| Characteristics | Patients, $n$ (%) |
|---|---|
| Age (yr), median (range) | 56 (19-70) |
| Gender | |
| Male | 21 (65.6) |
| Female | 11 (34.4) |
| ECOG performance status | |
| 0 | 16 (50) |
| 1 | 11 (34.4) |
| 2 | 5 (15.6) |
| Underlying liver disease | |
| HBV | 23 (71.9) |
| Alcohol | 2 (6.3) |
| Other | 7 (21.8) |
| Prior therapy | |
| Surgery | 4 (12.5) |
| Ablation | 5 (15.6) |
| TACE | 19 (59.4) |
| TACE + radiotherapy | 4 (12.5) |
| Child Pugh score | |
| A | 22 (68.8) |
| B | 10 (31.2) |
| Cirrhosis | |
| No | 20 (62.5) |
| Yes | 12 (37.5) |
| HBV-DNA | |
| < 1.0e3 cps/mL | 16 (69.6) |
| ⩾ 1.0e3 cps/mL | 7 (30.4) |
| Portal vein thrombosis | |
| No | 25 (78.1) |
| Yes | 7 (21.9) |
| Median AFP (ng/mL) | |
| ⩾ 400 | 22 (68.8) |
| < 400 | 10 (31.2) |
| Metastasis | |
| Lung | 9 (28.1) |
| Bone | 6 (18.8) |
| Adrenal gland | 9 (28.1) |
| Lymph node | 3 (9.4) |
| Peritoneum | 3 (9.4) |
| Other | 2 (6.2) |

ECOG: Eastern Cooperation Oncology Group; HBV: Hepatitis B virus; TACE: Transarterial chemoembolization; AFP: Alpha fetoprotein.

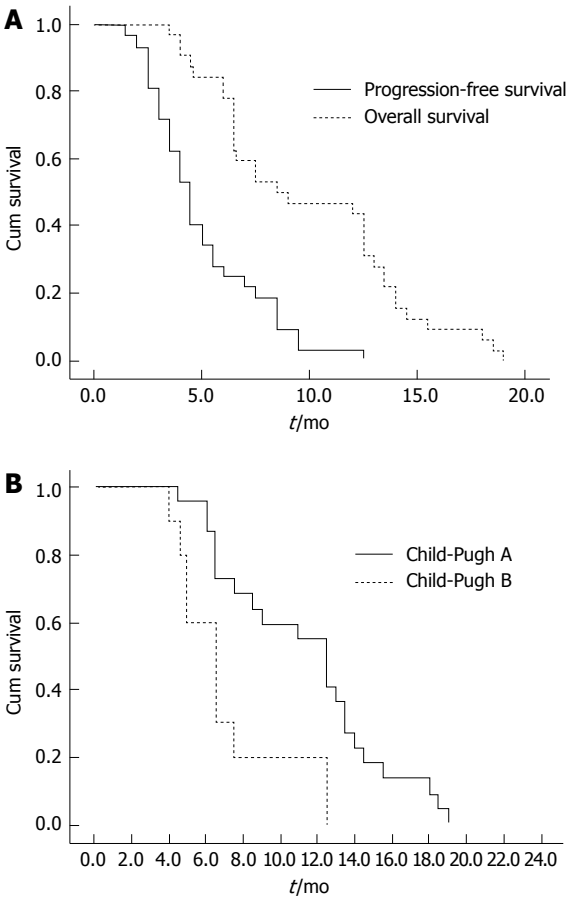


**Figure 1 Kaplan-Meier estimation.** A: Progression-free survival and overall survival ($n$ = 32); B: Overall survival by Child-Pugh class group ($n$ = 32).

In total, 142 cycles of CapeOx were administered, with a median of four cycles (range 1-9 cycles) per patient. Dose reductions including oxaliplatin in 9/32 patients (28.1%) were due to grade 1/2 toxicities, and capecitabine in 9/32 patients (28.1%) because of grade 3/4 toxicities. Oxaliplatin was discontinued in 2 patients with grade 3 neurotoxicity. Thirty-two patients were assessable for efficacy and toxicity. The median follow-up duration was 15 mo (range 12-20 mo). At the cut-off date of March 31, 2012, 27 patients died due to tumor progression and one patient died of myocardial infarction. Four patients were still alive (3 patients with disease progression). OR was 21.9% ($n$ = 7), the stabilization rate was 40.6% ($n$ = 13), and the DCR was 62.5%. The responses lasted 4-19 mo (median, 6 mo). Median TTP was 4.2 mo (95%CI: 2.5-7.4), and the median OS time was 9.2 mo (95%CI: 6.5-17.8; Figure 1A). The 1-year survival rate was 43.6% (95%CI: 29-66). In a multivariate analysis, OS was significantly longer in patients with a Child-Pugh class A compared with class B patients ($P$ = 0.014), with a median OS of 10.1 mo *vs* 5.4 mo (Figure 1B), and there were trends towards longer OS ($P$ = 0.065) in patients without portal vein tumor thrombosis. There were no significant effects of age, gender, PS, cirrhosis, metastatic sites, and level of AFP or HBV-DNA on OS (data not shown). Among the 22 patients with elevated AFP levels at baseline (⩾ 400 ng/mL), the level fell by more than 50% during therapy in 6 patients (27.3%). Moreover, 2 of the 5 patients whose initial PS was equal to 2, improved to 1 after two cycles of treatment. Three of 23 patients treated with lamivudine therapy switched to entecavir therapy because the level of HBV-DVA had exceeded the baseline level (⩾ 1.0e3 cps/mL) during treatment.

### Safety

Toxicities are summarized in Table 2. Treatments were generally well tolerated in the majority of patients, and there were no treatment-related deaths. Thirty-two patients were assessable in toxicity. Grade 3-4 toxicity occurred in 11 patients (34.4%). Hematologic toxicity was the most common severe toxicity, including thrombocytopenia (6.3%; no bleeding events) and neutropenia (6.3%; fever in only one case). Grade 3 neurotoxicity was the most common severe non-hematologic toxicity, affecting 2 patients (6.39%), whereas grades 1 and 2 neurotoxicity

**Table 2 Treatment-related toxicities in 32 patients**

| Adverse event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Neutropenia | 2 | 2 | 1 | 1 |
| Thrombocytopenia | 4 | 3 | 1 | 1 |
| Anemia | 5 | 1 | 0 | 0 |
| Nausea/vomiting | 6 | 3 | 1 | 0 |
| Mucositis | 4 | 2 | 0 | 0 |
| Stomatitis | 3 | 2 | 1 | 0 |
| Diarrhoea | 0 | 1 | 1 | 0 |
| Transaminases | 7 | 3 | 1 | 0 |
| Hyperbilirubinemia | 2 | 0 | 0 | 0 |
| Neurotoxicity | 5 | 8 | 2 | 0 |
| Hand-foot syndrome | 4 | 2 | 1 | 0 |

Hepatitis B virus DNA level (real-time polymerase chain reaction, Abbott, Wiesbaden, Germany).

occurred in 6 (18.8%) and 3 (9.4%) patients, respectively.

### Additional treatments

Nine patients had received additional treatments due to tumor progression. Six patients with bone metastasis received local palliative radiotherapy, and three patients received sorafenib therapy.

## DISCUSSION

Sorafenib is currently considered standard of care systemic therapy for patients with advanced HCC. The use of sorafenib is based on phase Ⅱ and phase Ⅲ data in patients with metastatic HCC, with the treatment group showing close to a 3-mo survival advantage over the non-treated group in Child-Pugh class A[3,19]. In contrast, Child-Pugh class B patients did not seem to derive any benefit from sorafenib in phase Ⅲ trials[5,20]. Similarly, in a series of Asian patients, only patients with a score of B7 seemed to benefit from sorafenib, at the cost of higher rates of bleeding events[21]. National Institute for Health and Clinical Excellence does not recommend sorafenib for patients with advanced hepatocellular carcinoma, because it does not provide enough benefit to patients to justify its high cost[22]. In addition, the results of SOFIA study showed that only dose-adjusted, but not full-dose sorafenib was a cost-effective treatment compared to best supportive care in intermediate and advanced HCC. There was no cost-effective treatment for patients with intermediate HCC who were not eligible to or failed locoregional therapy even if they were treated with dose-adjusted sorafenib[23].

The survival rates of HCC patients have risen greatly concomitant with the progress in diagnostic and treatment methods. However, the survival prognosis for treatment-resistant progressive liver cancers is extremely poor[24]. Although surgical resection was used as treatment for pulmonary metastasis from HCC, the treatment might be only beneficial for patients with few than three lung lesions[25]. Chemotherapy used in combination with interferon is considered to be effective but lacks adequate scientific evidence[26].

From general point of view and in line with previous reports[12,27,28], CapeOx seems feasible and suitable for palliative care in patients with advanced HCC. With lack of renal toxicity of oxaliplatin[29], the low incidence of myelosuppression observed with capecitabine[30], the synergistic anti-tumor activity and safety of capecitabine and oxaliplatin combination in advanced HCC[31], and the absence of dose adjustment required for both agents in case of hepatic dysfunction, make the CapeOx regimen attractive in advanced HCC patients with cirrhosis or chronic HBV infection[15,32]. A multicenter, open-label, phase Ⅱ study of CapeOx reported a response rate of 6% and a disease control rate of 72%[33], however, patients who had not undertaken local therapies were eligible for this study. For patients with extrahepatic metastasis from HCC, systemic chemotherapy of carboplatin and 5-FU had demonstrated a statistically significant improvement in OS (10.7 mo *vs* 5.1 mo) in comparable patients with non-chemotherapy[34].

For these patients who had extrahepatic metastasis after local treatments and who had no significant alteration of their liver function, palliative chemotherapy can be delivered with tolerable toxicity[35]. Recently, research combining the use of CapeOx and cetuximab for advanced HCC reported an RR of 12.5%, TTP of 3.3 mo and overall survival of 4.4 mo[36]. Another phase Ⅱ trial of CapeOx with bevacizumab for advanced HCC in 2011 showed tumor response and disease control rates of 20% and 77.5%, respectively[31]. The median OS and PFS were 9.8 and 6.8 mo, respectively. In our study, although only the cytotoxic chemotherapy drugs oxaliplatin and capecitabine were used for patients with extrahepatic metastasis, the result was encouraging for both efficacy and toxicity. Partial response was seen in 21.9% patients, and 62.5% had their disease controlled. The study also showed a median TTP of 4.2 mo and a median OS of 9.2 mo in a patient population of 50% with Eastern Cooperation Oncology Group PS 1-2, and more than 31% of the patients with Child- Pugh class B disease status.

Obviously the underlying liver cirrhosis increases the risk of severe adverse events as many chemotherapeutic drugs are metabolized or eliminated *via* the liver. Moreover, severe complications might occur if a cytotoxicity-related side effect appears on a cirrhotic liver. Certain causes of the underlying cirrhosis, such as hepatitis B virus infection, may be reactivated after chemotherapy induced immunosuppression, producing an additive toxic effect[37].

In conclusion, palliative chemotherapy can be delivered to patients with extrahepatic metastasis from HCC following local treatments with tolerable toxicity. However, the efficacy was not satisfactory. More effective systemic chemotherapy regimens are needed for this subgroup of patients.

## ACKNOWLEDGMENTS

We would like to express our heartfelt gratitude to Dr. Chel-

sea Gilft and Dr. Koung Fang Pei (MD, Anderson Cancer Center) for modifying the language of the manuscript.

## COMMENTS

### Background

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide. The overall 5-year survival rate for all HCC patients has remained no more than 5%. Sorafenib is the first agent to demonstrate a survival advantage over supportive care in HCC. Nevertheless, in a relatively fit group of sorafenib-treated patients (95% Childs-Pugh A), median survival was only 10.7 mo. The purpose of this study was to evaluate the safety and efficacy of the capecitabine-oxaliplatine combination (CapeOx) in patients with extrahepatic metastatic HCC following local treatments.

### Research frontiers

Local recurrence and distant metastasis are still obstacles in further improvement of outcome in HCC patients after local treatments. Doxorubicin, until recently considered the standard chemotherapeutic for HCC, is associated with an objective response rate of approximately 10%. In this study, the authors aimed to valuate the efficacy and safety of CapeOx regimen in patients with extrahepatic metastasis from HCC following local treatments.

### Innovations and breakthroughs

Sorafenib is currently considered standard of care systemic therapy for patients with advanced HCC, but results from recent several studies showed it not suitable in some patients with advanced HCC. In this study, CapeOx regimen showed modest anti-tumor activity in metastatic HCC and tolerated toxicities.

### Applications

This study may represent a future strategy for therapeutic intervention in the treatment of patients with extrahepatic metastasis from HCC following local treatments even if with liver cirrhosis.

### Terminology

Capecitabine is an orally administered, tumor-selective fluoropyrimidine that mimics continuous infusion of 5-fluorouracil. Oxaliplatin s a new platinum complex, diaminocyclohexane compound, which is thought to result from inhibition of DNA synthesis in cancer cells. The combination of oxaliplatin and capecitabine has also shown some promise in HCC because both drugs are tolerated in the setting of hepatic dysfunction.

### Peer review

This study is an uncontrolled phase 2 evaluation of capecitabine and oxaliplatin for locally controlled HCC with extrahepatic metastases involving 32 patients, the majority of whom were hepatitis B virus infected and non-cirrhotic. The majority of patients' metastases were pulmonary or intra-abdominal with 6/32 being confined to bone. Twenty-eight percent of patients required dose reduction of capecitabine due to grade 3/4 toxicity but only 2 grade 3 oxaliplatin toxicities occurred. Ninety-seven percent of patients died or manifested tumor progression. Median time to tumor progression was 4.2 mo and median overall survival was 9.2 mo. This is an interesting prospective study on efficacy of CapeOx combination regimen for extrahepatic metastasis of HCC following local treatments, and gives a practical point of view in management of these patients.

## REFERENCES


1 **Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]

2 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078]

3 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

4 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

5 **Hollebecque A**, Cattan S, Romano O, Sergent G, Mourad A, Louvet A, Dharancy S, Boleslawski E, Truant S, Pruvot FR, Hebbar M, Ernst O, Mathurin P. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. *Aliment Pharmacol Ther* 2011; **34**: 1193-1201 [PMID: 21958438 DOI: 10.1111/j.1365-2036.2011.04860.x]

6 **Pressiani T**, Boni C, Rimassa L, Labianca R, Fagiuoli S, Salvagni S, Ferrari D, Cortesi E, Porta C, Mucciarini C, Latini L, Carnaghi C, Banzi M, Fanello S, De Giorgio M, Lutman FR, Torzilli G, Tommasini MA, Ceriani R, Covini G, Tronconi MC, Giordano L, Locopo N, Naimo S, Santoro A. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. *Ann Oncol* 2013; **24**: 406-411 [PMID: 23041587 DOI: 10.1093/annonc/mds343]

7 **Patt YZ**, Hassan MM, Aguayo A, Nooka AK, Lozano RD, Curley SA, Vauthey JN, Ellis LM, Schnirer II, Wolff RA, Charnsangavej C, Brown TD. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. *Cancer* 2004; **101**: 578-586 [PMID: 15274071]

8 **Goldberg RM**, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; **22**: 23-30 [PMID: 14665611]

9 **Qin S**, Bai Y, Ye S, Fan J, Lim H, Cho JY, Thongprasert S, Chao Y, Rau K, Sun Y. Phase III study of oxaliplatin plus 5-fluorouracil/leucovorin (FOLFOX4) versus doxorubicin as palliative systemic chemotherapy in advanced HCC in Asian patients. *J Clin Oncol* 2010; **28** Suppl: Abstract 4008

10 **Lee JO**, Lee KW, Oh DY, Kim JH, Im SA, Kim TY, Bang YJ. Combination chemotherapy with capecitabine and cisplatin for patients with metastatic hepatocellular carcinoma. *Ann Oncol* 2009; **20**: 1402-1407 [PMID: 19502532 DOI: 10.1093/annonc/mdp010]

11 **Kakolyris S**, Souglakos J, Kouroussis C, Androulakis N, Samonis G, Vardakis N, Amarantidis K, Agelaki S, Mavroudis D, Xenidis N, Georgoulias V. Dose escalation study on oxaliplatin and capecitabine (Xeloda) in patients with advanced solid tumors. *Oncology* 2004; **66**: 253-259 [PMID: 15218291]

12 **Coriat R**, Mir O, Cessot A, Brezault C, Ropert S, Durand JP, Cacheux W, Chaussade S, Goldwasser F. Feasibility of oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX-4) in cirrhotic or liver transplant patients: experience in a cohort of advanced hepatocellular carcinoma patients. *Invest New Drugs* 2012; **30**: 376-381 [PMID: 20798975 DOI: 10.1007/s10637-010-9525-0]

13 **Coskun U**, Buyukberber S, Yaman E, Uner A, Er O, Ozkan M, Dikilitas M, Oguz M, Yildiz R, B DY, Kaya AO, Benekli M. Xelox (capecitabine plus oxaliplatin) as neoadjuvant chemotherapy of unresectable liver metastases in colorectal cancer patients. *Neoplasma* 2008; **55**: 65-70 [PMID: 18190244]

14 **Ho C**, Ng K, O'Reilly S, Gill S. Outcomes in elderly patients with advanced colorectal cancer treated with capecitabine: a population-based analysis. *Clin Colorectal Cancer* 2005; **5**: 279-282 [PMID: 16356306]

15 **Twelves C**, Glynne-Jones R, Cassidy J, Schüller J, Goggin T, Roos B, Banken L, Utoh M, Weidekamm E, Reigner B. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. *Clin Cancer Res* 1999; **5**: 1696-1702 [PMID: 10430071]

16 **Berretta M**, Lleshi A, Di Benedetto F, Bearz A, Spina M, Tirelli U. Oxaliplatin and capecitabine (Xelox) in association with highly active antiretroviral therapy in advanced

hepatocarcinoma HIV/HCV-infected patients. *Ann Oncol* 2006; **17**: 1176-1177 [PMID: 16798837 DOI: 10.1093/annonc/mdj140]

17 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]

18 **Kautio AL**, Haanpää M, Kautiainen H, Leminen A, Kalso E, Saarto T. Oxaliplatin scale and National Cancer Institute-Common Toxicity Criteria in the assessment of chemotherapy-induced peripheral neuropathy. *Anticancer Res* 2011; **31**: 3493-3496 [PMID: 21965767]

19 **Abou-Alfa GK**, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 4293-4300 [PMID: 16908937]

20 **Ozenne V**, Paradis V, Pernot S, Castelnau C, Vullierme MP, Bouattour M, Valla D, Farges O, Degos F. Tolerance and outcome of patients with unresectable hepatocellular carcinoma treated with sorafenib. *Eur J Gastroenterol Hepatol* 2010; **22**: 1106-1110 [PMID: 20300004 DOI: 10.1097/MEG.0b013e3283386053]

21 **Zhou L**, Xu ZX, Zhou Y, Feng Y, Zhou XG, Xiang HF, Roy VA. Structure-charge transport relationship of 5,15-dialkylated porphyrins. *Chem Commun* (Camb) 2012; **48**: 5139-5141 [PMID: 22517491 DOI: 10.1002/cncr.27543]

22 **National Institute for Health and Clinical Excellenc**. NICE technology appraisal guidance 189 - Sorafenib for the treatment of advanced hepatocellular carcinoma. Available from: URL: www.nice.org.uk/guidance/TA189

23 **Cammà C**, Cabibbo G, Petta S, Enea M, Iavarone M, Grieco A, Gasbarrini A, Villa E, Zavaglia C, Bruno R, Colombo M, Craxì A. Cost-effectiveness of sorafenib treatment in field practice for patients with hepatocellular carcinoma. *Hepatology* 2013; **57**: 1046-1054 [PMID: 23299720 DOI: 10.1002/hep.26221]

24 **Llovet JM**, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Brú C, Rodés J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62-67 [PMID: 9862851]

25 **Lee CY**, Bae MK, Park IK, Kim DJ, Lee JG, Choi JS, Han KH, Chung KY. Surgical resection for pulmonary metastasis from hepatocellular carcinoma: analysis of prognosis in relation to primary control. *J Surg Oncol* 2010; **101**: 239-243 [PMID: 20127898 DOI: 10.1002/jso.21487]

26 **Chung YH**, Song IH, Song BC, Lee GC, Koh MS, Yoon HK, Lee YS, Sung KB, Suh DJ. Combined therapy consisting of intraarterial cisplatin infusion and systemic interferon-alpha for hepatocellular carcinoma patients with major portal vein thrombosis or distant metastasis. *Cancer* 2000; **88**: 1986-1991 [PMID: 10813709]

27 **Louafi S**, Boige V, Ducreux M, Bonyhay L, Mansourbakht T, de Baere T, Asnacios A, Hannoun L, Poynard T, Taïeb J. Gemcitabine plus oxaliplatin (GEMOX) in patients with advanced hepatocellular carcinoma (HCC): results of a phase II study. *Cancer* 2007; **109**: 1384-1390 [PMID: 17330837]

28 **Mir O**, Coriat R, Boudou-Rouquette P, Ropert S, Durand JP, Cessot A, Mallet V, Sogni P, Chaussade S, Pol S, Goldwasser F. Gemcitabine and oxaliplatin as second-line treatment in patients with hepatocellular carcinoma pre-treated with sorafenib. *Med Oncol* 2012; **29**: 2793-2799 [PMID: 22427209 DOI: 10.1007/s12032-012-0208-x]

29 **Boda-Heggemann J**, Hofheinz RD, Weiss C, Mennemeyer P, Mai SK, Hermes P, Wertz H, Post S, Massner B, Hieber U, Hochhaus A, Wenz F, Lohr F. Combined adjuvant radiochemotherapy with IMRT/XELOX improves outcome with low renal toxicity in gastric cancer. *Int J Radiat Oncol Biol Phys* 2009; **75**: 1187-1195 [PMID: 19409725 DOI: 10.1016/j.ijrobp.2008.12.03]

30 **Sharma R**, Rivory L, Beale P, Ong S, Horvath L, Clarke SJ. A phase II study of fixed-dose capecitabine and assessment of predictors of toxicity in patients with advanced/metastatic colorectal cancer. *Br J Cancer* 2006; **94**: 964-968 [PMID: 16552436]

31 **Sun W**, Sohal D, Haller DG, Mykulowycz K, Rosen M, Soulen MC, Caparro M, Teitelbaum UR, Giantonio B, O' Dwyer PJ, Shaked A, Reddy R, Olthoff K. Phase 2 trial of bevacizumab, capecitabine, and oxaliplatin in treatment of advanced hepatocellular carcinoma. *Cancer* 2011; **117**: 3187-3192 [PMID: 21264839 DOI: 10.1002/cncr.25889]

32 **Honecker FU**, Brümmendorf TH, Klein O, Bokemeyer C. Safe use of oxaliplatin in a patient with metastatic breast cancer and combined renal and hepatic failure. *Onkologie* 2006; **29**: 273-275 [PMID: 16783902]

33 **Boige V**, Raoul JL, Pignon JP, Bouché O, Blanc JF, Dahan L, Jouve JL, Dupouy N, Ducreux M. Multicentre phase II trial of capecitabine plus oxaliplatin (XELOX) in patients with advanced hepatocellular carcinoma: FFCD 03-03 trial. *Br J Cancer* 2007; **97**: 862-867 [PMID: 17876335]

34 **Hirano G**, Sakurai K, Sohda T, Kunimoto H, Yotsumoto K, Fukunaga A, Iwashita H, Ueda S, Yokoyama K, Morihara D, Takeyama Y, Sakamoto M, Irie M, Iwata K, Shakado S, Sakisaka S. Systemic chemotherapy using carboplatin and 5-fluorouracil for extrahepatic metastasis of hepatocellular carcinoma. *Hepatogastroenterology* 2012; **59**: 2264-2268 [PMID: 22389294]

35 **Lee JO**, Kim DY, Lim JH, Seo MD, Yi HG, Oh DY, Im SA, Kim TY, Bang YJ. Palliative chemotherapy for patients with recurrent hepatocellular carcinoma after liver transplantation. *J Gastroenterol Hepatol* 2009; **24**: 800-805 [PMID: 19175825 DOI: 10.1111/j.1440-1746.2008.05672.x]

36 **Sanoff HK**, Bernard S, Goldberg RM, Morse MA, Garcia R, Woods L, Moore DT, O'Neil BH. Phase II Study of Capecitabine, Oxaliplatin, and Cetuximab for Advanced Hepatocellular Carcinoma. *Gastrointest Cancer Res* 2011; **4**: 78-83 [PMID: 22043322]

37 **Yeo W**, Lam KC, Zee B, Chan PS, Mo FK, Ho WM, Wong WL, Leung TW, Chan AT, Ma B, Mok TS, Johnson PJ. Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. *Ann Oncol* 2004; **15**: 1661-1666 [PMID: 15520068]

**P- Reviewers** Cabibbo G, Kaplan DE, Sharma MK, Strosberg JR
**S- Editor** Gou SX **L- Editor** Ma JY **E- Editor** Li JY

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327