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RESEARCH PAPER

First-line treatment with hepatic arterial infusion plus capecitabine vs capecitabine alone for elderly patients with unresectable colorectal liver metastases

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ABSTRACT

This study aimed to compare the efficacy and safety of HAI fluoropyrimidine (FUDR)/capecitabine or single capecitabine as first-line treatment for elderly patients with unresectable colorectal liver metastases (CLMs). Fifty-one elderly patients with liver-only CLMs were eligible for enrollment. Patients were divided into HAI FUDR /capecitabine group and single capecitabine group randomly. The primary endpoint was median survival time (MST), defined as the time from the date of catheter implantation to the date of death or the date of the last follow-up. The secondary endpoint was objective antitumor response and adverse events. The HAI pump was implanted before chemotherapy. All patients received a 3-week cycle of oral capecitabin. In Group A, the RR and DCR were both 95.8%. In Group B, the RR and DCR were 48.1% and 81.5%, respectively. There was significant difference between the RRs of the 2 groups ($P < 0.001$). But there was no significant difference between the DCRs of the 2 groups ($P = 0.053$). There was a statistical difference between the MSTs of the 2 groups (18.5 $vs.$13 months, $P = 0.0312$). HAI FUDR combined with oral capecitabine as the first-line treatment for elderly patients with CLMs has promising efficacy and safety.

Introduction

Colorectal cancer (CRC) occupies the fourth place of diagnosed malignant disease over the world.[1] The liver is the most common site of CRC metastasis, with 15% of patients presenting with liver metastases as diagnosis and almost 60% developing liver metastases during the disease course.[2]

Colorectal liver metastases (CLMs) are the major reason for the failure to treatment.[3] Though hepatic resection has been proposed as the standard protocol for curing CLMs, 75–85% of patients with liver-only metastases are considered unresectable.[4,5] Hence in patients with CLMs, the choices of treatment strategy vary according to factors such as the urgency of operation on the primary lesion, liver function, patient's performance condition, as well as the operation conditions of the institute.[6] Especially in the absence of symptoms, primary tumor resection is not recommended.[7]

Previous studies have suggested that the combination of hepatic arterial infusion (HAI) and systematic chemotherapy can obviously reduce the tumor burden of CRC and thus increase the resection rate.[8-10] And this combination is better than systematic chemotherapy alone.[11,12]

The hepatic extraction rate with HAI of floxuridine (FUDR) is 95% in patients with unresectable CLMs. HAI FUDR can increase the possibility of tumor response and might improve liver function, thus producing minimal systemic toxicity.[13,14] From Oct. 2010, HAI FUDR has been applied to treat patients with CLMs in our department.

Capecitabine (Xeloda; Hoffmann-La Roche Inc., Nutley, NJ) is an oral fluoropyrimidine with similar efficacy to bolus 5-fluorouracil/folinic acid as the first-line treatment for metastatic CRC. The efficacy and safety of capecitabine as single-agent therapy has been established based on comparisons with bolus 5-fluorouracil/folinic acid regimens. Besides, the oral administration is more convenient.[15,16]

In this article we compare the efficacy and safety of HAI FUDR/capecitabine or single capecitabine in patients with CLMs. We aim to provide evidences for the application of HAI/capecitabine treating patients with CLMs clinically.

Results

Patient baseline characteristics

Between June 2011 and May 2014, we treated 51 consecutively eligible patients with CLMs were enrolled in our department. Patients were divided into HAI/capecitabine group and single capecitabine group based on their wishes. Of these patients, 24 were in Group A (HAI + oral capecitabine) and 27 in Group B (oral capecitabine alone). There were no statistical differences

Table 1. Baseline of patients' characteristics (n = 51).

Characteristics	Total (n = 51)	Group A (n = 24)	Group B (n = 27)	P
Age (year)				0.781
Median	78	78	77.5	
Range	75–82	75–80	75–82	
Sex				0.778
Male	33	15	18	
Female	18	9	9	
Performance status				0.540
0	16	9	7	
1	26	12	14	
2	9	3	6	
Time to liver metastases				0.546
Synchronous	21	9	7	
Metachronous	30	15	20	
Site of primary cancer				0.404
Colon	28	10	15	
Rectum	23	14	12	
Lobulor involvement				0.264
Bilobar	27	15	12	
Unilobar	24	9	15	
Number of lesions				0.555
≤.5	19	7	12	
> 5	32	17	15	
Baseline of CEA				0.405
> 200 ng/ml	22	12	10	
< 200 ng/ml	29	12	17	

Abbreviations: CEA, carcinoembryonic antigen; LDH, lactate dehydrogenase
Group A: hepatic arterial infusion of fluorouracil + capecitabine; Group B: capecitabine alone

among the clinicopathological characteristics of the 2 groups (**Table 1**). No patients were lost to follow-up.

Response

In Group A, there were 6 complete responses (CRs), 17 partial responses (PRs), no stable disease (SD) and 1 progressive disease (PD), the response rate (RR) and disease control rate (DCR) were both 95.8%. In Group B, there were no CR, 13 PRs, 9 SDs and 5 PDs, the RR and DCR were 48.1% and 81.5%, respectively. There was significant difference between the RRs of the 2 groups ($P < 0.001$). But there was no significant difference between the DCRs of the 2 groups ($P = 0.053$). See **Table 2**.

Survival

Group A: n = 24, 8 alive, 16 died, median survival time 18.5 months, follow-up 8-42 months. Group B: n = 27, 7 alive, 20

Table 2. Objective response evaluated by CT scan [n (%)].

	Group A (n = 24)	Group B (n = 27)	P
Complete response	6 (25.0)	0 (0)	
Partial response	17 (70.8)	13 (48.1)	
Stable disease	0 (0)	9 (37.5)	
Progressive disease	1 (0.42)	5 (18.5)	
Response rate	95.8%	48.1%	< 0.001
Disease control rate	95.8%	81.5%	0.053

Group A: hepatic arterial infusion of fluorouracil + capecitabine; Group B: capecitabine alone

died, median survival time (MST) 13 months, follow-up 4-26 months. There was a statistical difference between the MSTs of the 2 groups ($P = 0.0312$). See **Fig. 2**.

Adverse events

Grade 3 adverse events are evaluated according to National Cancer Institute Common Toxicity Criteria version 3. In Group A, 1 patient experienced neutropenia, 3 experienced alanine aminotransferase/aspartate transaminase (ALT/AST) elevation, 4 experienced nausea and vomiting, 4 experienced abdominal pain, 3 experienced diarrhea, 2 experienced gastric ulceration, 1 experienced paresthesia, 1 experienced fatigue, 3 experienced hand and foot syndrome. In Group B, 1 patient experienced neutropenia, 1 experienced ALT/AST elevation, 2 experienced nausea and vomiting, 3 experienced abdominal pain, 1 experienced diarrhea, 1 experienced paresthesia, 1 experienced fatigue, 4 experienced hand and foot syndrome. No patient had catheter occlusion during the follow-up period. See **Table 3**.

Discussion

The theoretical basis of HAI therapy is that the preferential blood supply from the hepatic artery to CLMs allows for delivery of agents through a HAI catheter for eligible patients with liver-only or liver-dominant disease. During the past 5 years, our group has treat hundreds of patients with CLMs, most of who received a hepatic response and thus might be treated with subsequent surgical therapy. The images of a typical patient are showed in **Fig 1**.

The treatment strategy for patients with unresectable CLMs depends on the symptoms and resectability of the primary tumor. All the criteria for these patients should include 1) true unresectable disease, signifying massive tumor extent which results in inability to achieve a margin-negative resection; and 2) relative unresectable disease such as multiple hepatic metastases and synchronous disease.[17] The enrolled patients in the present study were all bore relative unresectable disease, so they were possible to receive other therapy modalities including HAI.

These hepatic metastases are discovered synchronously in 15%–25% of patients,[18,19] while 20%–25% of patients metachronously develop hepatic tumors.[20] So the rate of synchronous over metachronous CLMs is consistent with that in our study.

HAI chemotherapy as the first-line treatment for patients with unresectable CLMs is not common. Notably, the current evidence does not support the use of HAI FUDR alone for treatment of patients with unresectable CLMs.[21] While being combined with systematic chemotherapy, HAI therapy not only improves the RR, but also increases the resectability.[22]

Two meta-analyses observed a survival advantage (27% relative risk reduction)[23] and a obviously higher RR of HAI (41% vs. 14%) [24] comparing with systemic therapy alone. Besides, CALGB 9481 trial compared the administration of HAI pump vs. systematic chemotherapy. Results suggested that HAI FUDR had a significant longer overall survival (24.4 months vs. 20.0 months) and higher RR (47% vs. 24%). These results confirmed the advantage of HAI to systematic chemotherapy when same
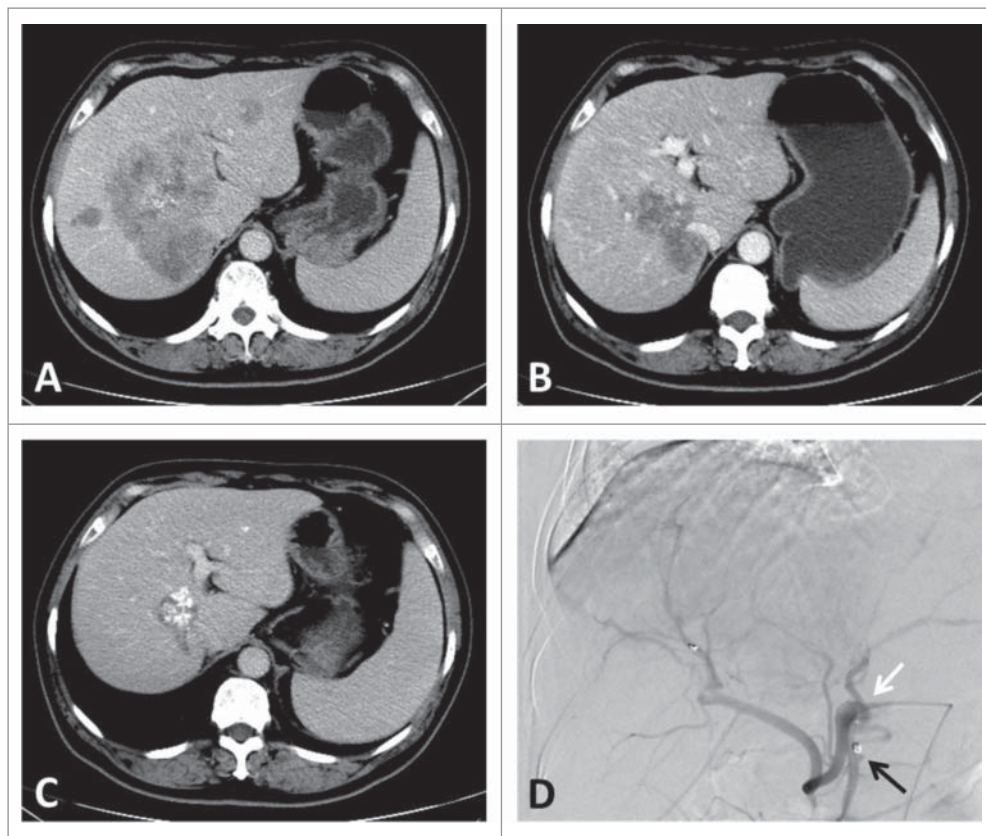
Figure 1. A typical patient's images of CT scan and angiography through infusion catheter. CT image showing (A). liver metastases involving all vessels at baseline; (B). 3 months after HAI pump implantation; (C). 1 year after HAI pump implantation. Angiography showing (D). the infusion catheter with side-hole (white arrow) is fixed into the gastroduodenal artery with metallic coils (black arrow).

agents were used.[12] The mode of this trial is similar with ours, in which we also applied the same agent, capecitabine, in both 2 groups. And likewise we observed that difference between the RRs of the 2 groups were statistical significant. In the present study, the RR and DCR of HAI/capecitabine were both 95.8%, which is much higher than other trials. The high response rate seen in this study may be due to the use of HAI FUDR.

Besides and more importantly, the results from the major endpoint was even more promising, with a significant longer

Table 3. Grade 3 adverse events.

Grade 3 adverse event	Group A (n = 24)	Group B (n = 27)
Hematologic		
Neutropenia	1 (4.2)	1 (3.7)
Hepatic		
ALT/AST	3 (12.5)	1 (3.7)
Gastrointestinal		
Nausea and vomiting	4 (16.7)	2 (7.4)
Abdominal pain	4 (16.7)	3 (11.1)
Diarrhea	3 (12.5)	1 (3.7)
Ulcer	2 (8.3)	0 (0)
Neurologic		
Paresthesia	1 (4.2)	1 (3.7)
Constitutional		
Fatigue	1 (4.2)	1 (3.7)
Hand and foot syndrome	3 (12.5)	4 (14.8)

Adverse events are evaluated according to National Cancer Institute Common Toxicity Criteria version 3
Group A: hepatic arterial infusion of fluorouracil + capecitabine; Group B: capecitabine alone
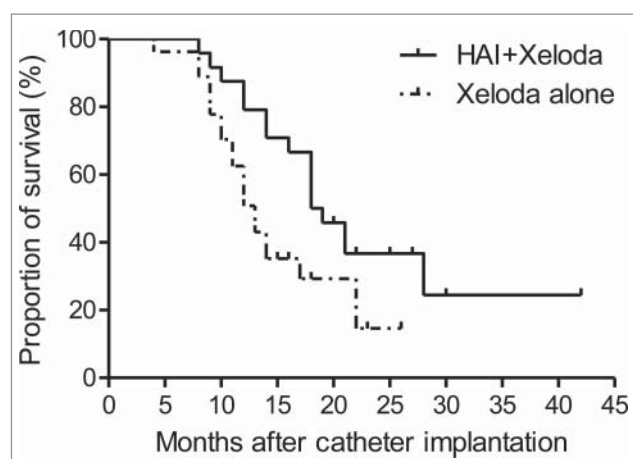
overall survival in HAI/capecitabine was observed. In a clinical trial, the median survival in the group receiving combined therapy was 68.4 months compared to 58.8 months for those receiving systemic therapy alone.[11] We believe that the increased part of overall survival is contributed to HAI FUDR mostly.

Hence, our results provide evidences for the combination of HAI FUDR and chemotherapeutics for patients with CLMs. Furthermore, HAI therapy not only helps improve the RR of chemotherapy, but also increases the magnitude of tumor shrinkage, which can improve the resectability.[25,26]

Generally speaking, the adverse events were tolerable. Adverse events were possibly related to extrahepatic perfusion of FUDR, although the main branch vessels from the arteries associated with the stomach or duodenum were routinely embolized before catheter implantation. Gastrointestinal and hepatotoxicity are main side effects of HAI therapy. It seemed that the occurrence of adverse events was inevitable to some extent but fortunately, these adverse events were reversible in all patients and no patients permanently discontinued HAI therapy. As for hand and foot syndrome, it was supposed to be due to the administration of capecitabine. Fortunately, technical (related to the catheter, port, or pump) adverse events did not occur.

All the enrolled subjects were elderly patients who preferred a safer and more convenient regimen with slighter adverse events, which was the reason that we chose capecitabine. Actually, most of these elderly patients could not endure combined regimens containing oxaliplatin and irinotecan. On the other

Figure 2. Survival curves for patients in Capecitabine and Capecitabine/HAI groups. HAI/Capecitabine group: n = 24, 8 live, 16 died, median survival time 18.5 months, follow-up 8–42 momths; Capecitabine group: n = 27, 7 live, 20 died, median survival time 13 months, follow-up 4–26 momths ($P=0.0312$).

hand, oxaliplatin and irinotecan have been investigated thoroughly in clinical trials focusing on chemotherapy for colorectal liver metastases. However, oral chemotherapeutic drugs were investigated much less. Moreover, most of these elderly patients elder than 75 y old could not endure or do not wish to receive combined regimens containing oxaliplatin and irinotecan. Elderly Chinese patients tend to receive oral chemotherapy. Hence, we set the arm of capecitabine for elderly patients. Generally speaking, capecitabine leads to slighter or less adverse events. In present China, only a small portion of patients with colorectal cancer are able to afford the expenses of molecular targeted agents such as cetuximab and bevacizumab.

According to the follow-up data, patients were administered completely on their own. There were only 47 patients enrolled and fortunately all were compliant with oral capecitabine. There were some adverse events occurred, but no patient ended the therapy during the treatment. In future studies with larger sample sizes, it is not possible to reach a 100%-compliance.

The purpose of this study is mainly to confirm the advantage of hepatic arterial infusion and the results do achieve the expectation. The dihydropyrimidine dehydrogenase enzyme is responsible for the detoxifying metabolism of fluoropyrimidines, a class of drugs that includes FUDR and capecitabine.[21,27] Capecitabine leads to a systemic anti-tumor effect but HAI FUDR aims to provide a locally durable accumulation of anti-tumor response via the pump. The mechanism of the 2 treatment modalities were different.

This is a prospective study and has limitations because of its small sample and lack a control group with similarly unresectable CLMs, which was initially treated with modern systemic chemotherapy alone.

Patients and Methods

Patient enrollment

This prospective, non-randomized study was approved by the ethics committees of the participating medical institutes and conducted according to the principles of the Declaration of

Helsinki and Good Clinical Practice Guidelines. All patients gave their written informed consent before enrollment.

Patients were potentially eligible if they 1) had liver metastases considered technically unresectable 2) had no detectable extrahepatic metastatic lesions; 3) had not undergone prior treatment; 4) were not receiving concurrent treatment that interfered with the study evaluation; 5) had hematologic and chemistry parameters in acceptable ranges including: absolute neutrophil count $\geq 1.2 \times 10^9$/L, direct bilirubin ≤ 1.5 times the instituteal upper normal limit (UNL), AST ≤ 2.5 times the UNL; the creatinine below the UNL or the creatinine clearance of higher than 60 mL/min/1.73 m^2 if the creatinine was above the UNL [28,29]; 6) were at least 18 y and not pregnant or breast-feeding women; 7) had a Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 1; and 8) were having inadequate calorie and fluid intake.

The primary endpoint was MST, defined as the time from the date of catheter implantation to the date of death or the date of the last follow-up. The secondary endpoint was objective antitumor response and adverse events.

Pretreatment evaluation

Pretreatment evaluation included a complete history, physical examination, and laboratory studies including complete blood cell, AST, total bilirubin, alkaline phosphatase, lactate dehydrogenase and carcinoembryonic antigen were obtained within 1 week before therapy. Computed tomography (CT) scans of the chest, abdomen, and pelvis were obtained within 6 weeks before therapy. Hepatic computed tomography angiogram (CTA) including visualization of the celiac and superior mesenteric arteries was also obtained before HAI pump implantation.

Data of sex, age, time of liver metastases, location of primary cancer, number of metastatic lesions, baseline level of tumor markers, adverse events related to treatment, survival time from time of catheter implantation were collected. The treatment protocol was determined by the multi-disciplinary treatment group composed of an oncologist, an interventional therapy specialist, a radiologist and a surgeon.

HAI pump implantation

The operation of HAI pump implantation was performed under the monitoring of CTA in a standard digital subtraction angiography operation room. After local injection of anesthetic, the Seldinger technique was applied to gain access to the right femoral artery. Arteriography for the celiac trunk and superior mesenteric artery was performed to reveal the hepatic arterial anatomy.

In patients with multiple hepatic arteries, all the hepatic arteries except the largest one were embolized to redistribute the hepatic arterial flow to enable the use of a single indwelling catheter to infuse chemotherapeutic agents to the entire liver.[30] The gastroduodenal artery, right gastric artery (if necessary, left gastric artery or dorsal pancreatic artery) were embolized using metallic coils (Tornade, Cook, Bloomington, IL, USA) to prevent extrahepatic drug distribution and gastroduodenal injury caused by the chemotherapeutic agents. To avoid dislodgment of the catheter tip and hepatic arterial occlusion, the infusion

catheter (Celsite, B. Braun, Chasseneuil, France) with side-hole was fixed into the gastroduodenal artery with metallic coils (n = 36) or inserted into the peripheral branch of the hepatic artery (n = 6) as described by Tanaka et al.[31] The position of the side hole was sited at the common hepatic artery to ensure that the chemotherapeutic agents infuse the entire liver from the side-hole. The proximal end of the catheter was connected to the injection port and the device was implanted in a subcutaneous pocket in the right inner thigh. After the administration of chemotherapeutic agents, the implanted port and indwelling catheter system were flushed and filled with 2 mL of heparin solution (1,000 IU/mL).

Once the catheter was in place, intraoperative assessment of perfusion was required by infusion of 5 mL of FUDR via the catheter or port. Postoperatively, a technetium sulfur colloid radionuclide liver scan was required to assess liver perfusion. HAI were kept performed synchronous with capecitabine until disease progression or patients' refusal.

Chemotherapy

All patients received a 3-week cycle of oral capecitabin. The day patients received HAI implantation was defined as day 0. Both of the HAI therapy and oral capecitabine were initiated on day 1, lasting on day 1–14. Floxuridine was delivered in a 14-day infusion at 1.5 $mg \cdot kg^{-1} \cdot d^{-1}$ divided by flow rate. Dexamethasone at 1 mg/m^2/day divided by flow rate was always placed in the pump with floxuridine heparin and saline. Oral capecitabine was administered at 1,000 mg/m^2 twice daily for 2 weeks. The first dose of capecitabine was given in the evening of day 1 and the last dose on the morning of day 15. The next cycle began on day 22.

If serious technical catheter-related problems, hepatic disease progression or severe toxicity did not occur, HAI were kept performed until disease progression or patients' refusal.

If a grade 1 or 2 adverse event related to FUDR occurred, HAI FUDR was held until clinical resolution. The FUDR dose was reduced if moderate chemical hepatitis or gastroduodenitis was noted. Dose reduction was based on the abnormal liver function tests in the preceding treatment cycle. FUDR administration was permanently discontinued if severe chemical hepatitis or biliary stricture was observed.

Patients who developed abdominal pain prompted workup received gastrointestinal endoscopy. If an ulcer or gastroduodenitis was observed, HAI therapy was held for 1 month and the dose of FUDR was reduced in subsequent cycles of HAI therapy. Resection of the primary colorectal tumor was indicated if obstruction or significant bleeding occurred.

Disease assessment and follow-up

Disease assessments (CT scan) were conducted within 28 d before starting study treatment and repeated after every 2 cycles according to the RECIST criteria [32] by investigators. Confirmation of response of therapy was required after at least 4 weeks. After completion of study treatment, patients were followed every 3 months until 5 y postregistration or death. Patients lost to follow-up were censored.

Statistical analysis

All statistical analyses were performed using SPSS 13.0 software (SPSS Inc., USA). Categorical variables were compared using χ^2 test. Continuous variables by compared by Wilcoxon's rank-sum test. The differences between the 2 groups were compared by χ^2 test. The survival curve was estimated using the Kaplan–Meier method. Survival curves were compared using the log-rank test. A P value less than 0.05 was considered statistically significant.

Conclusions

Our data show that initial HAI FUDR combined with oral capecitabine as the first-line treatment for patients with CLMs. The high RR, acceptable MST and tolerable adverse events are the advantage of the combination comparing with capecitabine. Future research should focus on the alteration of the agents in the combination. A multi-center randomized study is warranted to confirm the efficacy and safety of HAI therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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