ORIGINAL ARTICLE

Phase I/II study of irinotecan, UFT and leucovorin with hepatic arterial infusion using 5-FU in colorectal cancer patients with unresectable liver metastases

Tatsuro Yamaguchi · Hiroshi Matsumoto · Michiya Yasutome · Takeo Mori · Keiichi Takahashi

Abstract

Purpose   To evaluate the efficacy and tolerability of systemic chemotherapy with irinotecan (CPT-11), UFT and leucovorin (LV) combined with hepatic arterial infusion (HAI) consisting of 5-fluorouracil (5-FU) in colorectal cancer patients with unresectable liver metastases.

Methods   Patients were treated concurrently with escalating doses of intravenous CPT-11 (100, 120, and 140 mg/m^2) on day 1 of each 14-day treatment cycle, with oral UFT (300 mg/m^2 per day) and LV (75 mg/body per day) on days 1–7 of each cycle, and with HAI 5-FU (2,000 mg/week) on days 8–14 of each cycle.

Results   Twelve patients were enrolled in the phase I study. The maximum-tolerated dose was not reached. Consequently, the recommended dose of CPT-11 for the phase II study was determined to be 140 mg/m^2. Twenty-two patients were evaluated in the phase II study. Five patients experienced grade 3 neutropenia, two experienced grade 3 anorexia, two experienced nausea, and two experienced vomiting. An overall response was observed in 19 out of 22 patients (86.4%). The median progression-free survival period was 11.2 months, and the 3-year survival rate was 50.6%. Fourteen patients (63.6%) were ultimately able to undergo a complete liver resection.

Conclusions   Chemotherapy with CPT-11 and UFT/LV combined with HAI yielded a high response rate and enabled a significant proportion of patients with initially unresectable liver metastases to undergo surgical resection. Further trials are warranted.

Keywords   Colorectal cancer · Hepatic arterial infusion · Irinotecan · UFT · Leucovorin · Phase I/II study

Introduction

Colorectal cancer (CRC) is one of the most commonly occurring solid tumors in Japan as well as in western countries [1, 2]. Liver metastases develop in more than 30% of advanced colorectal cancer (CRC) patients. Surgical resection is the most effective treatment for liver metastases from CRC [3]. However, only 10–25% of CRC patients with liver metastases are candidates for liver resection because of the presence of extrahepatic disease or other medical conditions [4, 5].

Hepatic arterial infusion (HAI) is used for regional chemotherapy for colorectal liver metastases. Although HAI for the treatment of colorectal liver metastases results in a high response rate, its survival benefit seems to be minimal because of the development of extrahepatic disease [6]. Kerr et al. [7] reported that HAI monotherapy should not be administered outside of a clinical trial. On the other hand, the combination of systemic chemotherapy and HAI reportedly demonstrated good results in patients with unresectable colorectal liver metastases [8, 9]. The combination of systemic chemotherapy with HAI for unresectable colorectal liver metastases can be expected as a new treatment strategy, although no phase III evidence is available.

UFT is an oral fluoropyrimidine derivative containing tegafur and uracil in a 1:4 molar ratio. Tegafur is a 5-FU prodrug that is rapidly absorbed into the systemic circulation after oral administration and is converted to 5-FU in

T. Yamaguchi (✉) · H. Matsumoto · M. Yasutome ·
T. Mori · K. Takahashi
Department of Surgery, Tokyo Metropolitan Cancer
and Infectious Disease Center Komagome Hospital,
3-18-22 Honkomagome, Bunkyo-ku,
Tokyo 113-8867, Japan
e-mail: tatsuro@yamaguchi.email.ne.jp

the liver. Uracil is a dihydropyrimidine dehydrogenase inhibitor that enables a higher concentration of 5-FU to be attained [10, 11]. UFT with oral leucovorin (LV) has been shown to result in a survival outcome equivalent to that of intravenous 5-FU/LV in patients with metastatic CRC and with lower frequencies of hematological toxicities than 5-FU/LV [12, 13]. Moreover, phase II studies demonstrated the activity and feasibility of a combination regimen of irinotecan (CPT-11) and UFT/LV in patients with metastatic CRC [14, 15]. HAI using 5-FU is ineffective against extrahepatic disease because 5-FU is trapped by the liver, thereby promptly decreasing its extrahepatic concentration. Therefore, we selected CPT-11 and UFT/LV for use as a systemic chemotherapy, anticipating the efficacy of these drugs against extrahepatic disease. Consequently, chemotherapy with CPT-11 and UFT/LV combined with HAI was expected to lead to a high response with an adequate safety profile in patients with unresectable colorectal liver metastases.

In this study, we used 5-FU instead of floxuridine (FUDR) for HAI because a clear difference in clinical outcome has not been noted between 5-FU and FUDR and because FUDR has not yet been approved in Japan. The primary objectives of this phase I study were to estimate the maximum-tolerated dose (MTD) of biweekly intravenous CPT-11 and UFT/LV combined with HAI using 5-FU and to determine the recommended dose (RD) for the phase II study. In the phase II study, we evaluated the efficacy and tolerability of this chemotherapy regimen in patients with unresectable hepatic metastases from CRC.

Patients and methods

Eligibility criteria

The eligibility criteria were as follows: CRC patients with measurable unresectable liver metastases; no previous chemotherapy or radiotherapy for metastatic CRC; an interval of at least 6 months between the end of adjuvant chemotherapy and/or radiotherapy and enrollment in this study; an age of between 20 and 75 years; a predicted life expectancy >3 months; an Eastern Cooperative Oncology Group performance status ≤1; and adequate baseline organ functions, defined as follows: a leukocyte count <4,000/mm^3, a neutrophil count <2,000/mm^3, a platelet count <100,000/mm^3, a hemoglobin level <9.0 g/dL, a serum aspartate and alanine aminotransferase level ≤2.5× the upper limit of normal (ULN), a serum bilirubin level ≤1.5× ULN, and a serum creatinine level ≤ULN. All the patients provided their written informed consent. The study protocol and the informed consent forms were approved by the Institutional Review Board of Tokyo Metropolitan Cancer and Infectious Disease Center, Komagome Hospital.

Criteria for unresectable disease

Patients were considered to have unresectable liver metastases if the metastases involved all the hepatic segments or if the resection would have left behind an inadequate liver remnant. Neither bilobar disease nor the number of metastases was regarded as a contraindication for resection, provided that a complete resection was possible. Tumors that involved all three main hepatic veins or both inflow pedicles were also considered unresectable. All patient cases were reviewed at a multidisciplinary conference involving surgeons, radiologists, and medical oncologists.

Catheterization for hepatic arterial infusion

Catheterization for HAI was performed either surgically or radiologically. In the surgical procedures, the HAI catheter was positioned at the junction of the proper and common hepatic artery via the gastroduodenal artery; the distal gastroduodenal artery, the right gastric artery, the small branches supplying the stomach and duodenum, and all the accessory hepatic arteries were then ligated. In the radiological procedure, the HAI catheter was positioned in the gastroduodenal artery and the gastroduodenal artery was fixed using metallic coils to prevent the catheter from moving. The medical agents flowed out from side holes in the catheter. Similar to the surgical procedure, all unnecessary arteries were embolized with metallic coils.

Treatment

CPT-11 was administered intravenously over 90 min on day 1 of each treatment cycle. All the patients received prophylactic antiemetic premedication with 5-hydroxytryptamine-3 receptor antagonists prior to each dose of CPT-11. UFT was administered at a dosage of 300 mg/m^2 per day orally in three divided doses at all dose levels on days 1–7 of each 14-day treatment cycle at 1 h prior to or following a meal. LV was administered at a dosage of 75 mg/body per day at all dose levels with each dose of UFT. 5-FU in saline (2,000 mg/week) with heparin was continuously administered via the hepatic artery using an infusion pump on days 8–14 of each treatment cycle. This treatment was repeated until progression or discontinuation because of toxicity. Moreover, treatment was discontinued if we judged that the liver metastases could be resected. Second and subsequent cycles of treatment were administered when the leukocyte count was ≥3,000/mm^3, the neutrophil count was ≥1,500/mm^3, the number of platelets was ≥100,000/mm^3, and all non-hematological toxicities were <grade 2 (as defined by

the Common Terminology Criteria for Adverse Events, version 3.0); treatment was delayed if these criteria were not met, but not for more than 2 weeks. If the delay was longer than 2 weeks, the patient was withdrawn from the study. The doses were to be reduced in the event of grade 3/4 toxicity. The CPT-11 dose was to be reduced by 20 mg/m^2 in the event of a leukocyte count <2,000/mm^3, a neutrophil count <1,000/mm^3, a platelet count <75,000/mm^3, a serum bilirubin level >2.0 mg/dL, or a grade 3/4 non-hematological toxicity (excluding nausea, vomiting and anorexia). The UFT dose was to be reduced by 20%, in addition to the reduction in the CPT-11 dose, in the event of grade 3/4 stomatitis. No dose reduction schedule was used for LV and 5-FU (HAI).

Phase I study

Dose-limiting toxicity (DLT) during the first two treatment cycles was defined as follows: a leukocyte count <1,000/mm^3 and a neutrophil count <500/mm^3 or <1,000/mm^3 with a body temperature of over 38°C; a platelet count <25,000/mm^3; non-hematological toxicity (excluding nausea, vomiting and anorexia) ≥grade 3; and a treatment delay >2 weeks. The starting dose of CPT-11 was 100 mg/m^2 (level 1), and the subsequent planned dose levels were 120 mg/m^2 (level 2) and 140 mg/m^2 (level 3). We decided to use an upper dose limit of 140 mg/m^2 for CPT-11, instead of the maximum dose of 150 mg/m^2 approved for use in Japan, because the treatment schedule used in this study did not include any rest periods. At least three patients were entered at each dose level. If one of the three patients experienced a DLT, at least three more patients were enrolled at the same dose. If any DLTs occurred in the additional patients, then that dose level was concluded to be the MTD. The dose at one level lower than the MTD was used as the RD for the phase II study. At least six patients were treated at the RD.

Phase II study

In the phase II study, the primary objective was to determine the response rate. Secondary objectives were to evaluate progression-free survival (PFS), overall survival (OS) and safety. The pretreatment evaluation included a medical history and physical examination, a complete blood count, serum biochemical tests, urinalysis, echocardiogram, a chest X-ray, and computed tomography scans of the abdomen and other sites of disease. The ECOG performance status and laboratory findings, including complete blood counts and serum biochemical tests, were checked every week. Tumor response was assessed using computed tomography scans of the target lesion(s) every 4 or 6 weeks and at the end of treatment, according to the response evaluation criteria in solid tumors. The tumor responses were confirmed by a second evaluation at least 4 weeks later. The relative dose intensities (actual dose delivered/planned dose) for the different components of the treatment regimen were calculated for the phase II part of the study.

The sample size was calculated based on the method described by Fleming [16]. Among patients with unresectable colorectal liver metastases, the response rate to HAI has been reported to be approximately 40–50% [17]. The response rate to CPT-11 with 5-FU/LV was 40–50%, which was about 20% higher than that of 5-FU/LV alone for the treatment of metastatic CRC [18, 19]. We calculated the required sample size for the phase II study based on a target activity level of 70% and a minimum activity level of 40%. With a power of 90% and an one-sided significance level of 5%, a total of 22 patients were required. The PFS and OS were calculated from the first day of treatment using the Kaplan–Meier method.

Results

Phase I study

Twenty-eight patients were enrolled between March 2004 and December 2006; 12 of these patients were enrolled in the phase I study. The patient characteristics are listed in Table 1. No DLTs were observed within the first 2 treatment cycles at dose levels 1 and 2. At dose level 3, 2 patients experienced grade 3 neutropenia without a high-grade fever, 1 patient experienced grade 3 anorexia, and 1 patient experienced grade 3 nausea (Table 2). Because no DLTs were observed within the first 2 treatment cycles at dose level 3, the study did not reach what would have been considered the MTD of CPT-11. Consequently, the recommended dosages were 140 mg/m^2 of CPT-11, 300 mg/m^2 per day of UFT, 75 mg/body per day of LV, and, for HAI, 2,000 mg/week of 5-FU.

Phase II study

Sixteen patients were enrolled in the phase II study. The six patients treated at the RD during the phase I study were also included in the phase II analysis ($n = 22$) (Table 1). The median number of treatment cycles administered to the 22 patients was 12.9 (range 6–18). In one patient, the catheter got dislodged two cycles after the placement of the pump. HAI was terminated in two patients because of hepatic arterial thrombosis. The median relative dose intensity was 91.9% for CPT-11, 83.4% for UFT and 88.9% for 5-FU (via HAI).

A low frequency of severe toxicity was observed (Table 3). Five patients (23%) developed grade 3 neutropenia,

Table 1 Patient characteristics

Characteristics	Phase I (n = 12)	Phase II[a] (n = 22)
Age		
Median	60	60
Range	39–74	39–69
Gender		
Male/female	8/4	8/14
ECOG performance status		
0	11	22
1	1	0
Tumor location		
Colon	9	14
Rectum	3	8
Tumor differentiation		
Well	5	5
Non-well	7	16
Lymph node status		
pN0	5	4
pN1	4	6
pN2	3	11
Timing of liver metastases		
Synchronous	12	20
Metachronous	0	2
Number of liver metastases		
Mean	11.4	12.4
Range	3–40	3–35
Maximum diameter of liver metastases		
Mean	6.7	6.3
Range	2.0–12.0	2.0–12.0

ECOG Eastern Cooperative Oncology Group

[a] The six patients treated at the recommended dose during the phase I study were also included in the phase II analysis

2 (9%) experienced grade 3 anorexia, 2 (9%) experienced nausea, and 2 (9%) experienced vomiting. Eleven patients (50%) experienced diarrhea (all grades), but only 1 patient experienced grade 3 diarrhea. Severe hepatic toxicity and biliary sclerosis were not observed.

Among the 22 patients, 19 exhibited a partial response, providing an overall response rate of 86.4% (95% CI, 71.7–100%) (Table 4). Among the 19 responders, treatment was terminated in 14 patients because of a decision to undergo surgery. The complete (R0) hepatic resection rate was 63.6% (95% CI 40.7–82.8%). The median PFS was 11.2 months (Fig. 1a), the median OS had not been reached, and the 3-year survival rate was 50.6% at 24 months after the last patient enrollment (Fig. 1b).

Discussion

Chemotherapy for unresectable metastatic CRC has advanced remarkably with the introduction of systemic chemotherapy regimens containing 5-FU/LV combined with CPT-11 (FOLFIRI) or oxaliplatin (FOLFOX), and high response rates and prolonged median survival times exceeding 20 months have been obtained [20, 21]. In cases where the patient's condition improves to the extent of allowing secondary surgery to be performed after such chemotherapy, prolonged survival times of over 40 months have been reported (although the number of such cases is small) [21, 22]. A retrospective study by Bismuth et al. [4, 23] demonstrated that systemic chemotherapy allowed a hepatectomy to be performed in some cases with previously unresectable metastatic CRC, and that the 5-year survival rate in these cases was comparable to that of resectable cases of CRC with liver metastasis.

Fluoropyrimidine-based HAI for colorectal liver metastases is a local therapy that is expected to yield a high response rate. In Western countries, FUDR, which has been shown to yield higher hepatic extraction rates than 5-FU, is used for HAI [24]. Dexamethasone is used in combination with FUDR HAI to reduce the toxic effects of this drug on the liver [25]. However, fluoropyrimidine-based HAI cannot adequately suppress extrahepatic tumor recurrence, and treatment with this regimen alone cannot be expected to extend the survival period of the patients [26]. Therefore, HAI in combination with active systemic chemotherapy may serve as a useful strategy for the treatment of unresectable CRC patients with liver metastases (particularly cases without extrahepatic metastasis), because such a regimen would exert a strong and direct antitumor activity against liver metastases while simultaneously controlling extrahepatic metastases [27]. Kemeny et al. [28] conducted a phase I study of two treatment regimens (FUDR HAI with oxaliplatin/CPT-11, and FUDR HAI with oxaliplatin/5-FU/LV) in unresectable CRC patients with liver-only metastases. The results of Kemeny's study suggested that a regimen combining fluoropyrimidine-based HAI with active systemic chemotherapy promised to be a valid means of treating CRC patients with unresectable liver-only metastases.

In Japan, FUDR has not yet been approved for clinical use; therefore, 5-FU is generally used for HAI. For the systemic chemotherapy portion of this regimen, a combination of oral fluoropyrimidine (UFT/LV) and CPT-11 was utilized. In the present phase I study, the MTD of CPT-11 was determined while administering fixed dose levels of 5-FU via HAI (2,000 mg/week) and UFT/LV (UFT, 300 mg/m^2 per day; LV, 75 mg/body per day). Because the CPT-11 dose approved for use in Japan is 150 mg/m^2, we set the CPT-11 dose levels in this phase I study at 100, 120 and

Table 2 Major toxicities during the first two cycles in the phase I study

Toxicity	No. of patients											
	Level 1 (n = 3)				Level 2 (n = 3)				Level 3 (n = 6)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	1	1			1	1			1	2		
Neutropenia		2			2					1	2	
Anemia	1	2			2	1			4	1	1	
Thrombocytopenia	1								1			
Total bilirubin	1								1			
AST	1								2			
ALT									1			
ALP	1				1				3			
Creatinine					1							
Anorexia									1		1	
Nausea									3	1		
Vomiting											1	
Diarrhea												
Stomatitis					1							
HFS												
Alopecia												

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *HFS* hand-foot syndrome

Table 3 Major toxicities in the phase II study

Toxicity	No. of patients (n = 22)	
	All grades	≥Grade 3
Leukopenia	12	1
Neutropenia	15	5
Anemia	22	5
Thrombocytopenia	1	0
Total bilirubin	6	0
AST	13	0
ALT	9	0
ALP	13	0
Creatinine	3	0
Anorexia	17	2
Nausea	20	2
Vomiting	14	2
Diarrhea	11	1
Stomatitis	4	0
HFS	2	0
Alopecia	16	–

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *HFS* hand-foot syndrome

Table 4 Response rate in the phase II study

Response	No. of patients (n = 22)
CR	0
PR	19
SD	3
PD	0
Response rate	86.4%
95% CI	71.7–100

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *CI* confidence interval

140 mg/m². In a subsequently conducted phase II study, R0 hepatic resection was possible in 14 of the 22 patients. This rate of R0 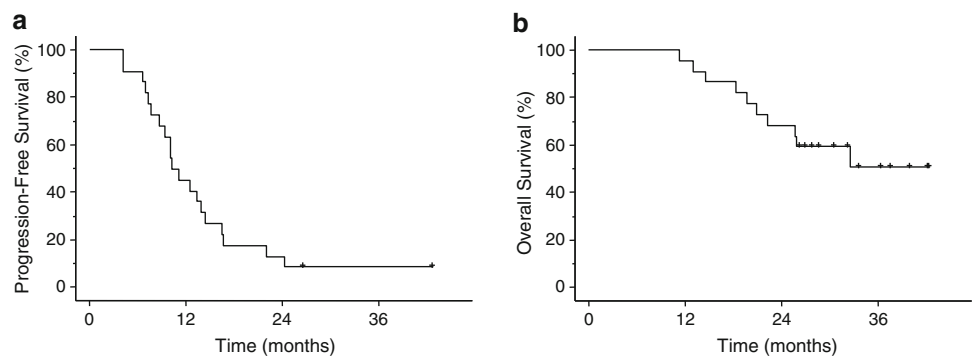hepatic resection, which was more than 60%, is unprecedented, considering the mean number and the mean maximum diameter of the liver metastases in the subjects of this study. Furthermore, the adverse events associated with this combined regimen were mild. Catheter-related complications consisted of catheter obstruction in one patient, hepatic arterial thrombosis in two patients, and bile duct bleeding in one patient. The catheter was successfully inserted in all the patients in this study, and no failures because of anatomical variations occurred in this series. Thus, this regimen may be a useful strategy for treating CRC patients with unresectable, liver-only metastases.

Recently, neoadjuvant systemic chemotherapy using FOLFIRI or FOLFOX has yielded high response rates (approximately 50%) and enabled one-third of patients with initially unresectable colorectal liver metastases to undergo

Fig. 1 **a** Progression-free survival (PFS) for phase II population (*n* = 22). The median PFS was 11.2 months. **b** Overall survival (OS) for phase II population (*n* = 22). The median OS had not been reached, and the 3-year survival rate was 50.6% at 24 months after the last patient enrolment

liver resection with curative intent [29–31]. The use of these systemic chemotherapy regimens containing 2-drug combinations of active cytotoxic agents is clinically feasible and, if R0 hepatic resection can be performed in a higher percentage of patients treated with these regimens, the prognosis of patients with initially unresectable liver metastases from CRC may be further improved. Our regimen involving a sequential combination of 5-FU HAI and systemic chemotherapy with UFT/LV/CPT-11 yielded a higher response rate and a higher R0 hepatic resection rate than systemic chemotherapy using FOLFIRI or FOLFOX alone. Irinotecan has been reported to be associated with steatohepatitis (20.2%), and oxaliplatin has been reported to be associated with sinusoidal dilation (18.9%) [32]. These morbidities have created obstacles to liver resection. In this study, no cases of steatohepatitis occurred.

In recent years, higher response rates and longer survival periods have been achieved in metastatic CRC patients through the use of biologic agents (bevacizumab, cetuximab, etc.) in combination with cytotoxic agents [33–36]. Therefore, when devising strategies for the treatment of patients with initially unresectable liver metastases from colorectal cancer, oncologists should focus on improving the response rate and the R0 hepatic resection rate by optimizing combinations of active chemotherapy regimens and biologic agents. The results from this study suggest that randomized controlled trials of the present regimen combined with biologic agents are warranted.

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