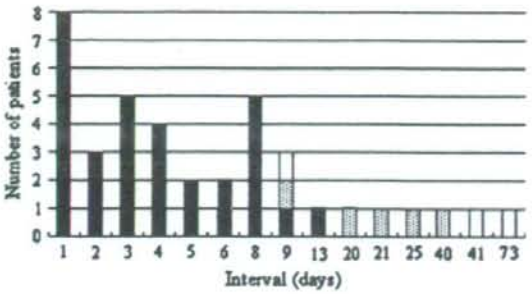


Fig. 2 Staining intensity of indocyanine green (ICG) and the intervals between endoscopic marking and surgery. The black box indicates the patients with strong staining. The dotted box represents the patients with weak staining, and the white box indicates those with no staining

All surgical resection specimens were evaluated by an experienced pathologist (S.I.), who examined the histologic slides for fibrosis, necrosis, and acute and chronic inflammation in the region of the marking.

Results

Figure 1B shows the typical green stain of ICG at the injection site with no adhesion of the surrounding tissues or organs. Altogether, 41 lesions or sites were marked with ICG before surgery for 39 patients (Table 1). One patient had double cancers at the transverse colon and the rectosigmoid junction, and the other patient had cancer with extensive diverticulosis at the sigmoid colon.

The locations of areas injected were the cecum ($n = 1$), the ascending colon ($n = 8$), the transverse colon ($n = 6$), the descending colon ($n = 2$), the sigmoid colon ($n = 15$), the rectosigmoid junction ($n = 5$), the upper rectum ($n = 3$), and the lower rectum ($n = 1$). The intraoperative ICG staining intensities and the intervals between the endoscopic marking and the operation for the 39 patients are shown in Fig. 2.

The ICG injection preceded surgery by a median of 4 days (range, 1–73 days). All 29 patients who underwent surgery 1–8 days after the marking had positive green staining, and the dye could be seen easily on the serosa of the colon or on the anterior wall of the rectum. After 9 days or more, however, the staining was obvious in only two of 10 patients. The positive rate of ICG staining was significantly different between these two groups ($p < 0.0001$, Fisher's exact test).

After 8 days, positive staining tended to grow weaker and fainter over time and finally to dissipate. For three patients with no staining, intraoperative colonoscopy was needed to detect the lesion. No significant difference in the staining was observed between the right- and left-sided colon, or between the operative procedures (laparoscopic versus open).

Table 1 Patient characteristics

Median age: years (range)	63.5 (41–84)
Sex (male/female)	22/18
Median interval between ICG marking and operation:days (range)	4.0 (1–73)
Marking site (total)	41[a]
Cecum	1
Ascending colon	8
Transverse colon	6
Descending colon	2
Sigmoid colon	15
Rectosigmoid junction	5
Upper rectum	3
Lower rectum	1
Tumor type	
Carcinoma	24
Adenoma	3
Post-EMR	13
Surgical procedure	
Laparoscopic surgery	18
Open surgery	22

ICG, indocyanine green; EMR, endoscopic mucosal resection

[a] 40 tumors and one site of diverculosis marked in 39 patients

None of the patients showed any preoperative adverse reactions to ICG injection such as fever, abdominal pain, or allergy symptoms. No complications were observed during surgery such as focal peritonitis, inflammatory pseudotumor, abscess, or adhesion, which have been described in reports addressing the use of India ink [3–8]. In one patient, ICG had spilled into the peritoneal cavity, however, and green stain on the serosa of the ascending colon without any adhesion also could be seen. The postoperative follow-up period was relatively short, but no postoperative complications, such as adhesion, ileus [9], have been encountered to date.

A histopathologic evaluation of the surgical specimens from the 39 patients showed no problematic fibrotic reaction, acute inflammation, or chronic inflammation, and no evidence of necrosis or microabscesses in any of the specimens. The pathologic diagnosis of tumor invasion was performed easily because ICG could be washed out of the tissue section.

Discussion

Endoscopic marking of intestinal lesions is essential when difficulty locating the lesion during a surgical resection is

anticipated. Clinically relevant complications of tattooing are considered to be rare [2]. Fu et al. [11] reported the rate of India ink leakage into the peritoneal cavity to be 1.8%, which is compatible with the rate in our ICG series (2.6%, 1/39). If India ink should leak, as shown in Fig. 1A, it can cause severe adhesion and bulky granuloma due to inflammation, thus making it difficult to perform a safe surgical resection, especially during a laparoscopic operation. Many reports also have shown complications of India ink tattooing [3–9]. Even if no serious complications are observed, it is difficult to collect all the scattered ink in the abdominal cavity. Consequently, foreign material is left permanently in the body.

In this study, no surgical adverse effects of ICG injection were encountered with the 39 patients. As shown in Fig. 2, the ICG marking was clearly observed in all 29 patients who underwent surgery within 8 days. However, 9 days or later, the staining was clearly seen in only two of the 10 remaining patients (20%), and the marking in three patients was undetectable. On the whole, positive staining of water-soluble ICG tended to be weaker and fainter over time, finally dissipating without forming foreign material, as described previously in animal models [14–16]. These results support the use of ICG as safe for endoscopic marking that can be reliably identified up to 8 days before surgery.

Generally, colonic tattooing has two aims: to mark small lesions for surgical resection and to mark the polypectomy site to facilitate location of the area during follow-up colonoscopy [10]. Several experimental studies comparing ICG and India ink for colonic tattooing in animals have reported that India ink is superior to ICG because of its higher visibility and longer duration [15, 16]. However, a longer duration is not always necessary for a surgical resection. Mechanical bowel preparation is indispensable when surgery is performed for small lesions that require palpation or intraoperative colonoscopy [21]. If endoscopic ICG marking is performed after mechanical preparation on the day before surgery, the number of preparations could be minimized. In a recent report on pancreatic surgery, ICG also was injected the day before surgery and reported to be a more suitable dye for tattooing of pancreatic lesions than India ink, with a much lower frequency of associated side effects [22].

Only a few reports to date describe human study of ICG as a tattooing agent for surgical resection. Hammond et al. [14], developing their previous study of 11 dogs, examined the surgical efficacy of ICG for 12 patients in 1993 [17]. They injected 1–2 ml of 1% ICG into the colonic wall under preoperative endoscopy, and all tattooed areas were surgically removed within 36 h. The dye was easily visible on the serosal surface of all the patients.

The current study investigated in detail the visibility and duration of ICG marking in 39 patients and extended the duration of ICG visibility in humans up to 8 days. However, ICG visibility depends not only on the intervals between endoscopic marking and surgery, but also on other various factors. Pericolonic fat, omentum, mesentery, or the posterior abdominal wall can block the surgeon's view of the injection site. New techniques of endoscopic tattooing may improve visualization of ICG compared with the conventional technique [11]. In addition, a larger total volume of submucosal injection is required. Circumferential four-quadrant injections may help to improve the visibility and durability of ICG staining [23].

Recently, possible toxicity from direct ICG staining of the retina in macular hole surgery was reported [24]. For 1,226 patients with intravenous ICG in ophthalmic imaging, Hope-Ross et al. [18] reported three mild adverse reactions, four moderate reactions, one severe reaction (0.05%), and no deaths. However, ICG has been used more than 40 years for a large number of patients and is considered to be highly safe [18–20]. An absolute contraindication to ICG injection, seen in only one patient without ICG marking in this study, is an allergy to iodide such as iodinated contrast material.

Askin et al. [13] reported that SPOT (GI Supply, Camp Hill, PA), approved for human use by the Food and Drug Administration, is a safe and effective marker because no adverse effects were observed after 118 SPOT injections for 113 patients. To our regret, SPOT has not yet been approved by the Ministry of Heath, Labor, and Welfare in Japan, so it cannot be tested here.

Endoscopic ICG marking represents a safe and useful method for preoperative marking of small colorectal lesions. It is suggested that ICG marking may be more suitable than India ink tattooing for surgical resections of the colorectum within 8 days after injection.

Acknowledgment The authors thank Dr. Shingo Ishiguro, Department of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases, for his technical assistance.

References

1. Ponsky JL, King JF (1975) Endoscopic marking of colonic lesions. Gastrointest Endosc 22:42–43
2. McArthur CS, Roayaie S, Waye JD (1999) Safety of preoperative endoscopic tattoo with India ink for identification of colonic lesions. Surg Endosc 13:297–400
3. Coman E, Brandt LJ, Brenner S, Frank M, Sablay B, Bennett B (1991) Fat necrosis and inflammatory pseudotumor due to endoscopic tattooing of the colon with India ink. Gastrointest Endosc 37:65–68
4. Park SI, Genta RS, Romeo DP, Weesner RE (1991) Colonic abscess and focal peritonitis secondary to India ink tattooing of the colon. Gastrointest Endosc 37:68–71
5. Lane KL, Vallera R, Washington K, Gottfried MR (1996) Endoscopic tattoo agents in the colon: tissue responses and clinical implications. Am J Surg Pathol 20:1266–1270

6. Dell'Abate P, Iosca A, Galimberti A, Piccolo P, Soliani P, Foggi E (1999) Endoscopic preoperative colonic tattooing: a clinical and surgical complication. Endoscopy 31:271–273
7. Hellmig S, Stüber E, Kiehne K, Folsch U (2003) Unusual course of colonic tattooing with India ink. Surg Endosc 17:521
8. Bahadursingh AM, Driver M, Koenig CL, Longo WE (2003) Inadvertent transmural India ink tattooing simulating intestinal infarction. Am J Surg 185:88–89
9. Yano H, Okada K, Monden T (2003) Adhesion ileus caused by tattoo marking: unusual complication after laparoscopic surgery for early colorectal cancer. Dis Colon Rectum 46:987
10. Hellmig S, Stüber E, Kiehne K, Kosmahl M, Folsch U (2005) What do we really know about the long-term safety of colonic tattooing? Gastrointest Endosc 61:186–187
11. Fu KI, Fujii T, Kato S, Sano Y, Koba I, Mera K, Saito H, Yoshino T, Sugito M, Yoshida S (2001) A new endoscopic tattooing technique for identifying the location of colonic lesions during laparoscopic surgery: a comparison with the conventional technique. Endoscopy 33:687–691
12. Sawaki A, Nakamura T, Suzuki T, Hara K, Kato T, Kato T, Hirai T, Kanemitsu Y, Okubo K, Tanaka K, Moriyama I, Kawai H, Katsurahara M, Matsumoto K, Yamao K (2003) A two-step method for marking polypectomy sites in the colon and rectum. Gastrointest Endosc 57:735–737
13. Askin MP, Waye JD, Fiedler L, Harpaz N (2002) Tattoo of colonic neoplasms in 113 patients with a new sterile carbon compound. Gastrointest Endosc 56:339–342
14. Hammond DC, Lane FR, Welk RA, Madura MJ, Borreson DK, Passinault WJ (1989). Endoscopic tattooing of the colon: an experimental study. Am Surg 55:457–461
15. Price N, Gottfried MR, Clary E, Lawson DC, Baillie J, Mergener K, Westcott C, Eubanks S, Pappas TN (2000) Safety and efficacy of India ink and indocyanine green as colonic tattooing agents. Gastrointest Endosc 51:438–442
16. Lee JG, Low AH, Leung JW (2000) Randomized comparative study of indocyanine green and India ink for colonic tattooing: an animal survival study. J Clin Gastroenterol 31:233–236
17. Hammond DC, Lane FR, Mackeigan JM, Passinault WJ (1993) Endoscopic tattooing of the colon: clinical experience. Am Surg 59:205–210
18. Hope-Ross M, Yannuzzi LA, Gragoudas ES, Guyer DR, Slakter JS, Sorenson JA, Krupsky S, Orlock DA, Puliafito CA (1994) Adverse reaction due to indocyanine green. Ophthalomol 101:529–533
19. Caeser J, Shaldon S, Chiandussi L, Guevara L, Sherlock S (1961) The use of indocyanine green in the measurement of hepatic flow and as a test of hepatic function. Clin Sci 21:43–57
20. Hiratsuka M, Miyashiro I, Ishikawa O, Furukawa H, Motomura K, Ohigashi H, Kameyama M, Sasaki Y, Kabuto T, Ishiguro S, Imaoka S, Koyama H (2001) Application of sentinel node biopsy to gastric cancer surgery. Surgery 129:335–340
21. Ram E, Sherman Y, Weil R, Vishne T, Kravarusic D, Dreznik Z (2005) Is mechanical bowel preparation mandatory for elective colon surgery? Arch Surgery 140:285–288
22. Ashida R, Yamao K, Okubo K, Sawaki A, Mizuno N, Nakamura T, Tajika M, Kawai H, Shimizu Y (2006) Indocyanine green is an ideal dye for endoscopic ultrasound-guided fine-needle tattooing of pancreatic tumors. Endoscopy 38:190–192
23. Hyman N, Waye JD (1991) Endoscopic four-quadrant tattoo for the identification of colonic lesions at surgery. Gastrointest Endosc 27:56–58
24. Ferencz M, Somfai GM, Farkas A, Kovacs I, Lesch B, Recsan Z, Nemes J, Salacz G (2006) Functional assessment of the possible toxicity of indocyanine green dye in macular hole surgery. Am J Ophthalmol 142:765–770

Cancer Chemother Pharmacol (2008) 61:275–281
DOI 10.1007/s00280-007-0471-2

ORIGINAL ARTICLE

A phase II study of irinotecan in combination with doxifluridine, an intermediate form of capecitabine, in patients with metastatic colorectal cancer

Takeshi Kato · Hideyuki Mishima · Masakazu Ikenaga · Kouhei Murata · Hideyuki Ishida · Mutsumi Fukunaga · Hirofumi Ota · Shusei Tominaga · Tadashi Ohnishi · Masahiro Amano · Kimimasa Ikeda · Masataka Ikeda · Mitsugu Sekimoto · Junichi Sakamoto · Morito Monden

Received: 27 November 2006 / Accepted: 14 March 2007 / Published online: 11 April 2007

Abstract The purpose of this study was to examine the efficacy of a combination treatment of sequential irinotecan and doxifluridine, an intermediate of capecitabine, evaluated by the response rate and safety in patients with metastatic colorectal cancer. In all, 60 metastatic colorectal cancer patients with measurable disease were enrolled. The schedule of the treatment consisted of a 90 min intravenous (IV) infusion of irinotecan 150 mg/m^2 for on days 1 and 15, and 600–1,000 mg/body of oral doxifluridine on days 3–14 and 17–28. Cycles were repeated every 35 days. A median of three cycles of the combination therapy (range 1–14 cycles) was administered. A total of 57 patients (95%) completed at least two cycles of the therapy without any dose reductions. There was one complete response and 23 partial responses with an overall response rate of 40% [95% confidence interval (CI): 28–53%]. A total of 19 patients had stable disease, 43(72%) achieved disease control. The median time to progression was 5.9 months and the median overall survival was 20.5 months. Ten (17%) and 17 (28%) patients developed Grade 3–4 leukopenia and neutropenia, respectively. Grade 3–4 fatigue was observed in 7(12%) patients, nausea in five (8%), vomiting in four (7%), and diarrhea,in three (5%) patients. No treatment-related deaths were noted during the study. From these results, the combination of sequential irinotecan and doxifluridine is considered to be an effective, easy-to-administer regimen with acceptable tolerability.

Keywords Combination chemotherapy · Colorectal cancer · Irinotecan · Doxifluridine · Phase II clinical trials

T. Kato (✉)
Minoh City Hospital 5-7-1 Kayano,
Minoh City, Osaka 562-8562, Japan
e-mail: takeshi_kato@maple.city.minoh.lg.jp

T. Kato · H. Mishima · M. Ikenaga · K. Murata · H. Ishida · M. Fukunaga · H. Ota · S. Tominaga · T. Ohnishi · M. Amano · K. Ikeda · M. Ikeda · M. Sekimoto · M. Monden
Multicenter Clinical Study Group of Osaka,
Colorectal Cancer Treatment Group, Suita, Osaka, Japan

M. Ikeda · M. Sekimoto · M. Monden
Graduate School of Medicine,
Department of Surgery, Osaka University,
Suita, Osaka, Japan

J. Sakamoto
Graduate School of Medicine,
Social Life Science, Young Leaders' Program,
Nagoya University, Nagoya, Aichi, Japan

Introduction

Colorectal cancer is one of the most frequently diagnosed malignancies in Japan. Surgical resection had been considered to be a therapy that offers a potential cure to patients with colorectal cancer. However, in spite of the curative resection, a considerable number of patients experience relapses of the disease and eventually die. In this regard, systemic chemotherapy aims to improve quality of life and prolong survival in patients with relapse and/or distant metastases.

5-Fluorouracil (5-FU) was developed approximately 50 years ago [10] and it has still been the key drug for the treatment of metastatic colorectal cancer. 5-FU has low oral bioavailability and prolonged infusion of the agent is the optimal administration method to exert high anti-tumor

activity. The combination of leucovorin (LV) with 5-FU significantly improved tumor response rates and time to progression compared to 5-FU alone [1].

Recent clinical study results showed significant activity of new cytotoxics, such as irinotecan and oxaliplatin, in monotherapy treatment for metastatic colorectal cancer. The addition of irinotecan or oxaliplatin to 5-FU/LV in randomised Phase III trials has shown high anti-tumor activity in patients with metastatic colorectal cancer [5, 6, 8, 21].

Although combination chemotherapy has been an important strategy in the treatment of metastatic colorectal cancer, some disadvantages accompany the treatment. First, higher treatment-related mortality and increased toxicity were observed, particularly when irinotecan is combined with bolus 5-FU/LV [13, 20]. Second, continuous infusion 5-FU/LV regimens require the use of implantable access devices and pumps, and sometimes have a negative influence on the patient's quality of life. For this reason, oral chemotherapy may represent one of the more convenient and acceptable treatments. Furthermore, some studies show that patients with advanced disease prefer oral chemotherapy rather than intravenous chemotherapy, provided that their efficacy remains the same [2, 14].

Doxifluridine is an oral fluoropyrimidine that was designed to generate 5-FU preferentially at the tumor site, via an enzymatic process that exploits the significantly higher activity of thymidine phosphorylase (TP) in tumors, compared with healthy tissue [11, 12]. Doxifluridine, which is an intermediate of capecitabine, has been shown to be effective in patients with colorectal cancer [17, 18]. Combining capecitabine instead of infusional 5-FU/LV with irinotecan or oxaliplatin is a rational alternative in terms of the practicability of the treatment. Phase II studies of capecitabine in combination with irinotecan or oxaliplatin have shown promising activity and a favorable safety profile in patients with metastatic colorectal cancer [4, 19]. When we started this study, oxaliplatin and capecitabine had not been approved in Japan, hence we chose irinotecan and doxifluridine in the present clinical trial for advanced colorectal cancer.

Irinotecan and doxifluridine both proved effective in colorectal cancer; however they can induce diarrhea. Preclinical and clinical Phase I studies have demonstrated the optimal dosing schedule [16]. According to the result of the previous study, we determined that irinotecan and doxifluridine would be better administered sequentially in order to protect from gastrointestinal toxicity. Based on the results of the Phase I trial, we decided to conduct a Phase II study to estimate the efficacy of a sequential irinotecan and doxifluridine combination regimen in patients with metastatic colorectal cancer.

Patients and methods

Patient eligibility

Patients with histologically confirmed recurrent or metastatic colorectal carcinoma were eligible for the study. Patients were required to have unresectable and measurable disease according to the Response Evaluation Criteria in Solid Tumor (RECIST) and aged between 20 and 74 years; Eastern Cooperative Oncology Group performance status (PS) $\leq$1; a life expectancy of at least three months; adequate bone marrow function, i.e., a neutrophil count $\geq$2,000 per μl, platelets $\geq$100,000 per μl and hemoglobin $\geq$8.0 g/dl; adequate hepatic function with serum bilirubin $\leq$1.5 mg/dl; glutamic oxaloacetic transaminase values (GOT) and glutamic pyruvic transaminases (GPT) $\leq$2 times the upper normal limit in the absence of hepatic metastases or $\leq$5 times the upper normal limit in the presence of metastasis; and adequate renal function with a creatinine value $\leq$1.5 mg/dl. Concurrent uncontrollable serious disease was not allowed in the eligibility criteria.

Exclusion criteria consisted of large amounts of ascites or pleural effusion, brain metastases, serious complications and any active malignancies (except for carcinoma-in-situ). Patients were excluded from the study if they had previously received more than two chemotherapy regimens or radiation therapy for advanced disease, or had a history of prior therapy with irinotecan.

The study was performed in accordance with the Helsinki Declaration. The study was previously approved by the Ethics Committees of each individual participating Institution. All patients provided written informed consent prior to entering this trial.

Treatment

The trial was conducted in 16 centers. Patients were registered before starting treatment in the coordinating center. Patients received 150 mg/m^2 per day of irinotecan on days 1 and 15, given as a 90 min IV infusion in 500 ml of normal saline or dextrose. Doxifluridine was administered orally three times daily, after every meal, on days 3–14 and 17–28. The daily dosages of doxifluridine were assigned on the basis of BSA: 600 mg (3 cap); <1.48 m^2, 800 mg (4 cap); 1.48–1.91 m^2, 1,000 mg (5 cap); >1.91 m^2. Each cycle of chemotherapy was given every 5 weeks if the patient's blood count had returned to normal and non-hematological toxicities had been resolved. Treatment was repeated for at least two cycles and was continued until disease progression or unacceptable toxicity was detected, or upon withdrawal of consent by the patient. The prophylactic use of anti-emetics was allowed. No prophylactic administration

using granulocyte colony-stimulating factor or diarrhea remedies was allowed.

Treatment was delayed until the neutrophil count had recovered to =1,500 per μl, the platelet count to =75,000 per μl, serum bilirubin to =1.5 mg/dl, serum creatinine to =2.0 mg/dl, and when there was no diarrhea = Grade 2 or infection. If toxicity required a dosing delay of more than 3 weeks, the patient would be withdrawn from the study for toxicity. If patients experienced Grade 3 toxicity or patients required a dosing delay of more than 2 weeks, the CPT-11 dose given was reduced to 120 mg/m^2. If patients experienced Grade 4 toxicity, the CPT-11 dose was reduced to 100 mg/m^2. If patients required a dosing delay of more than 3 weeks, the protocol treatment was stopped.

Evaluation procedures

Before initiating chemotherapy, all patients were assessed by physical examinations, PS assessment, routine hematology and biochemistry analyses, carcinoembryonic antigen (CEA) levels, and ECG. Radiological examinations (chest X-ray, CT scan and MRI of abdominal and thoracic measurable lesions) were performed within 2 weeks before the onset of treatment to serve as a baseline for serial evaluation of the patients' disease. Complete blood cell counts with platelet and differential counts were obtained weekly during chemotherapy. Serum chemistry and physical examination were repeated at least twice every cycle. All adverse reactions were recorded before each biweekly dose of chemotherapy. Radiological tumor parameter assessment and CEA levels were obtained every cycle and at the end of treatment. Tumor response was assessed according to RECIST criteria and confirmed at least 4 weeks later by the same evaluation. Progression-free survival (PFS) was determined by the interval from the date of registration to the date when disease progression was first documented, or to death due to any cause or to the last contact date. Overall survival (OS) was measured from the date of registration to death due to any cause or to the last contact date. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 2. For toxicity analysis, the worst data for each patient across all cycles were used.

Sample size and statistical considerations

The primary end point was response rate (RR), and the secondary objectives were OS, PFS and toxicity profiles. Dose intensity was calculated by dividing the actual dose of irinotecan given in each cycle by the dose originally scheduled for each patient.

Fifty-five patients were required for a single-stage Phase II trial, assuming that the expected RR would be 30% and the minimum acceptable RR 15% ($\alpha = 0.030$, $\beta = 0.190$). With 10% added for expected ineligible cases, a total of 60 patients were required.

OS and PFS were calculated using the Kaplan–Meier product-limit method from the date of registration. The 95% confidence intervals (95% CI) were also calculated. All analyses were performed using SAS for Windows, version 8.02 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

During the period between February 2003 and June 2004, a total of 60 patients were enrolled. All of the patients were assessable for efficacy and toxicity. Baseline patient characteristics are shown in Table 1. Patient ages ranged from 28 to 74, with a median age of 64 years; 87% of patients had a PS of zero and the others had a PS of one. There were 29 patients with colon carcinoma and 31 with rectal carcinoma as the primary tumor site. Twenty-three patients (38.3%) had synchronous metastatic diseases at first diagnosis, and the remaining 37 patients had recurrent metastatic diseases after surgery. Patients generally had distant metastases, with the most frequent distant sites including liver, lungs and peritoneal lymph nodes. A total of 30 patients (50%) had taken prior adjuvant chemotherapy with 5-FU derivatives.

Table 1 Patient characteristics

Characteristic	Number	%
Age (years) (mean and range)	64	28–74
Sex		
Male	37	62
Female	23	38
ECOG performance status		
0	52	87
1	8	13
Primary site		
Colon	29	48
Rectum	31	52
Metastatic site		
Liver	31	52
Lung	13	22
Lymph node	15	25
Others	6	10
Number of metastatic sites		
1	54	90
2	6	10
Previous adjuvant chemotherapy	30	50
Previous chemotherapy	11	18

Eleven patients (18%) had received prior chemotherapy with 5-FU derivatives for advanced disease, but terminated at least 4 weeks before registration into this study.

Treatment summary

A median of three cycles of combination therapy (range 1–14 cycles) was administered. A total of 57 patients (95%) completed at least two cycles of therapy without any dose reductions. The average dose intensity of irinotecan corresponded to 90%, and was maintained at more than 80% for seven cycles.

Response and survival

Response data are listed in Table 2. One patient obtained a complete response and 23 had a partial response. The overall RR achieved was 40% (95% CI: 28–53%), which was superior to the expected RR of 30%. Taking into account the 19 patients who had stable disease, 43 patients (72%) achieved disease control, defined as response or stable disease. Chemo-naïve patients had a good response rate (49.9%) compared to patients receiving second line therapy (29.3%).

With a median follow-up duration of 17.0 months, the median PFS was 5.9 (95% CI: 4.7–7.2) months. The median OS was 20.5 (95% CI: 14.3–31.3) months, and the one-year survival rate was 65% (Fig. 1). Chemo-naïve patients had slightly better survival (20.5 months) and PFS (6.0 months) compared to patients receiving second line therapy (19.5, 5.1 months, respectively). However, the differences were not significant.

Follow up treatment

For patients' refractory the irinotecan/doxifluridine regimen, mainly FOLFOX, hepatic arterial infusion (HAI), and some other regimens were adopted. The long survival rates obtained after progression may be related with the follow up regimens.

Table 2 Tumor response in 60 patients

Results	Number of patients	%
Complete response	1	2
Partial response	23	38
Stable disease	19	32
Progressive disease	14	23
Not evaluable	3	5
Overall response rate	40% (95% CI: 28–53%)	
Response rate according to receiving prior chemotherapy		
Yes		27
No		43

Toxicity

Toxicity assessments were available for all patients who received treatment. The incidence of the main toxic effects is listed in Table 3 as the maximum grade seen per patient. Ten (17%) patients developed grade 3 or 4 leukopenia, 17 (28%) developed neutropenia and one (2%) developed anemia. The most common Grade 3 or 4 non-hematological adverse events were fatigue (12%). Grade 3 or 4 nausea was seen in 5 (8%), vomiting in 4 (7%) and anorexia in 4 (7%) patients. Diarrhea at any grade was observed in 37% of patients, with Grade 3 or 4 in only 3 (5%) patients. No treatment-related deaths occurred during the study.

Discussion

The clinical efficacy of combination therapy with irinotecan and 5-FU is well established by phase III studies, showing that the addition of intravenous 5-FU/LV significantly improved anti-tumor activity and OS, compared to 5-FU/LV alone in patients with previously untreated metastatic colorectal cancer [6, 21]. Combination therapy with irinotecan and 5-FU, however, also resulted in increased toxicity such as diarrhea and neutropenia [13, 20], while it has been suggested that continuous infusion with 5-FU in combination with irinotecan may be a safer option than bolus 5-FU [15].

Doxifluridine, an oral fluoropyrimidine that converted to 5-FU predominantly in tumors [11, 12], is an intermediate form of capecitabine. Replacement of infused 5-FU/LV with oral doxifluridine is expected to be more efficacious and also reduce the toxicity of irinotecan and 5-FU combination therapy. Irinotecan in combination with doxifluridine might ameliorate the inconvenience and potential complications associated with the intravenous access required with infusional regimens. The primary toxicity of doxifluridine is gastrointestinal complications [17], which is the same as that for irinotecan [22]. On this point, the results of the preclinical study in the murine models suggested that the augmentation of gastrointestinal toxicity for the sequential dosing regimen, doxifluridine administered after intervals of a few days following the injection of irinotecan, was mild compared with that for the simultaneous dosing regimen [16]. Thus, we chose the sequential dosing regimen in which doxifluridine was administered two days after the administration of irinotecan. The hatus between irinotecan and doxifluridine (two days) could have alleviated the diarrhea commonly seen with the capecitabine-irinotecan regimen (simultaneous administration).

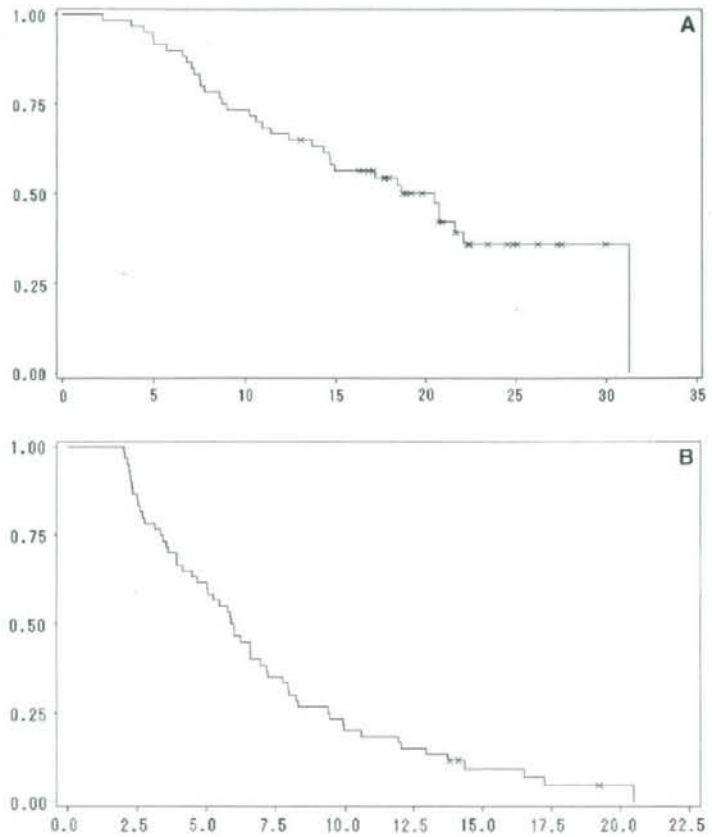


Fig. 1 Kaplan–Meier curves for overall survival and progression-free survival (total subjects = 60 patients). **a** Overall survival, death = 35 patients, median survival time = 20.5 months. **b** Progression free survival, progression/death = 57 patients, median PFS time = 5.9 months

In the present study, the sequential irinotecan and doxifluridine combination regimen was well tolerated, with fatigue the most frequently observed non-hematological toxicity. Grade 3–4 diarrhea occurred in only three patients (5%). This incidence was similar to that (5%) reported for 800 mg doxifluridine alone and slightly lower than that (13%) reported for 150 mg/m^2 irinotecan q2w alone. Compared to Phase II or III studies with irinotecan in combination with infusional 5-FU/LV regimens and oral fluoropyrimidines such as capecitabine, the incidence of Grade 3–4 diarrhea of 5% in our study is obviously lower than the 44% reported in the study by Douillard et al. [6], the 13% in the study by Tournigand et al. [23], and the 19% in the study with capecitabine by Rea et al. [19]. In addition, the average dose intensity of irinotecan corresponded to 90%, and was being maintained at more than 80% over seven cycles. Patient's informed consent for chemotherapy is essential in limiting the impact of toxicity, and clear instructions should be provided on the management of side effects, e.g., diarrhea, and the importance of seeking professional medical advice in case of severe complications.

The combination of irinotecan and doxifluridine is highly effective. The response rate and median survival time are comparable to the results for combinations of 5-FU and irinotecan in randomized studies: Saltz et al. (bolus 5-FU) reported 39% and 14.8 months [21]; Douillard et al. (infusional 5-FU), 41% and 17.4 months [6]; and Tournigand et al. (infusional 5-FU) 56% and 21.5 months [23], respectively. Besides efficacy, oral doxifluridine offers an advantage over infusional 5-FU/LV in terms of convenience. The response rates and time to progression in this study were similar to capecitabine and irinotecan [3, 7]. The median overall survival also seems to be closer to FOLFIRI [20] than other previously reported oral fluoropyrimidine regimens.

This trial has demonstrated that combining irinotecan and doxifluridine is an effective and well-tolerated regimen for patients with metastatic colorectal cancer when irinotecan is administered IV on days 1 and 15 in combination with doxifluridine administered on days 3–14 and 17–28 every 5 weeks. It produced an overall RR of 40% (95% CI: 28–53), a median PFS of 5.9 months (95% CI: 4.7–7.2) and a median OS of 20.5 months (95% CI: 14.3–31.3). With

Table 3 Maximum toxicity per patient (60 enrolled patients)

	NCI-CTC grade			All grades (%)
	G3	G4	≥G3 (%)	
Hematologic				
Neutropenia	12	5	17 (29)	30 (50)
Leukopenia	9	1	10 (17)	27 (45)
Anemia	0	1	1 (2)	1 (2)
Thrombocytopenia	0	0	0 (0)	1 (2)
AST	0	0	0 (0)	1 (2)
ALT	0	0	0 (0)	1 (2)
Non-hematologic				
Fatigue	6	1	7 (12)	36 (60)
Alopecia	–	–	–	30 (50)
Nausea	4	1	5 (8)	28 (47)
Diarrhea	3	0	3 (5)	22 (37)
Vomiting	3	1	4 (7)	12 (20)
Anorexia	4	0	4 (7)	7 (12)
Dysgeusia	0	0	0 (0)	3 (5)
Neuropathy	0	0	0 (0)	1 (2)
Abdominal pain	0	0	0 (0)	1 (2)
Headache	0	0	0 (0)	1 (2)
Rash	0	0	0 (0)	1 (2)
Stomatitis	0	0	0 (0)	1 (2)
Epigastralgia	0	0	0 (0)	1 (2)
Dehydration	1	0	1 (2)	1 (2)

respect to time to progression in this study (median PFS = 5.9 months), it is longer than 5FU/LV or capecitabine alone [24]. It is slightly shorter than a combination of CAPIRI or CAPOX [9]. The relatively shorter progression free survival could be related to inclusion of second line therapy patients whose PFS was 5.1 months. Besides, 72% of patients achieved stable disease and, overall, the regimen produced good symptom resolution.

In conclusion, the present study confirmed the potential efficacy of the sequential irinotecan and doxifluridine regimen without augmentation of gastrointestinal toxicity. We expect that combining irinotecan with doxifluridine would be more preferable than a combination of irinotecan and infusional 5-FU/LV with regard to the convenience of oral administration of doxifluridine and practicability with similar efficacy and less toxicity.

Since capecitabine is not approved for mCRC in Japan, We performed the preliminary examinations of irinotecan combination therapy with doxifluridine, a precursor substance of capecitabine, which has already been approved and utilized as a chemotherapeutic agent in Japan. We are planning to conduct an examination evaluating a capecitabine and irinotecan combination compared with doxifluridine and irinotecan, as soon as capecitabine is approved in Japan.

Acknowledgments This work was supported in part by the nonprofit organization, Epidemiological and Clinical Research Information Network (ECRIN). We would like to thank Ms. Chigusa Abe, Nahomi Iwahori and Chieko Takeuchi for devoting logistic support to this clinical trial.

References

1. Advanced Colorectal Meta-Analysis Project (1992) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 10:896–903
2. Borner MM, Schoffski P, de Wit R et al (2002) Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. Eur J Cancer 38:349–358
3. Borner MM, Bernhard J, Dietrich D et al (2005) A randomized phase II trial of capecitabine and two different schedules of irinotecan in first-line treatment of metastatic colorectal cancer: efficacy, quality-of-life and toxicity. Ann Oncol 16:282–288
4. Cassidy J, Tabernero J, Twelves C et al (2004) XELOX (capecitabine plus oxaliplatin): active first-line therapy for patients with metastatic colorectal cancer. J Clin Oncol 22:2084–2091
5. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
6. Douillard JY, Cunningham D, Roth AD et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet 355:1041–1047
7. Fuchs C, Marshall J, Mitchell E et al (2006) A randmized trial of first-line irinotecan/fluoropyrimidine combinations with or without celecoxib in metastatic colorectal cancer (BICC-C). J Clin Oncol Proc ASCO 24:18s
8. Giacchetti S, Perpoint B, Zidani R et al (2000) Phase III multicenter randomised trial of oxaliplatin added to chronomodulated fluorouracil–leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136–147
9. Grothey A, Jordan K, Kellner O et al (2004) Capecitabine/irinotecan (CapIri) and capecitabine/oxaliplatin (CapOx) are active second-line protocols in patients with advanced colorectal cancer (ACRC) after failure of first-line combination therapy: results of a randomized phase II study. J Clin Oncol Proc ASCO 22:14s
10. Heidelberger C, Chaudhuri NK, Danneberg P et al (1957) Fluorinated pyrimidines: anew class of tumor-inhibitory compounds. Nature 179:663
11. Ishitsuka H, Miwa M, Takemoto K, Fukuoka K, Itoga A, Maruyama HB (1980) Role of uridine phosphorylase for antitumor activity of 5'-deoxy-5-fluorouridine. Gann 71:112–123
12. Kono A, Hara Y, Sugata S, Karube Y, Matsushima Y, Ishitsuka H (1983) Activation of 5'-deoxy-5-fluorouridine by thymidine phosphorylase in human tumors. Chem Pharm Bull (Tokyo) 31:175–178
13. Ledermann JA, Leonard P, Seymour M (2001) Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. N Engl J Med 345:145–146
14. Liu G, Franssen E, Fitch MI, Warner E (1997) Patient preferences for oral versus intravenous palliative chemotherapy. J Clin Oncol 15:110–115
15. Meta-Analysis Group in Cancer (1998) Toxicity of fluorouracil in patients with advanced colorectal cancer: effect of administration schedule and prognostic factors. J Clin Oncol 16:3537–3541
16. Mishima H, Kato T, Yanagisawa M et al (2005) Sequential treatment with irinotecan and doxifluridine: Optimal dosing schedule in murine models and in a phase I study for metastatic colorectal cancer. Chemotherapy 51:32–39

17. Niitani H, Kimura K, Saito T et al (1985) Phase II study of 5'-deoxy-5-fluorouridine (5'-DFUR) on patients with malignant cancer: Multi-institutional cooperative study (in Japanese). Jpn J Cancer Chemother 12:2044–2051
18. Ota K (1988) Multicentre cooperative phase II study of 5'-deoxy-5-fluorouridine in the treatment of colorectal cancer. J Int Med Res 16(suppl 2):19B–20B
19. Rea DW, Nortier JWR, Ten Bokkel Huinink WW et al (2005) A phase I/II and pharmacokinetic study of irinotecan in combination with capecitabine as first-line therapy for advanced colorectal cancer. Ann Oncol 16:1123–1132
20. Rothenberg ML, Meropol NJ, Poplin EA, Van Cutsem E, Wadler S (2001) Mortality associated with irinotecan plus bolus fluorouracil/leucovorin: summary findings of an independent panel. J Clin Oncol 19:3801–3807
21. Saltz LB, Cox JV, Blanke C et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905–914
22. Shimada Y, Yoshino M, Wakui A et al (1993) Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. J Clin Oncol 11:909–913
23. Tournigand C, André T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 22:229–237
24. Van Cutsem E, Hoff PM, Harper P et al (2004) Oral capecitabine vs intravenous 5-floorouracil and leucovorin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 90:1190–7

癌と化学療法

VOL.35(2008)

癌と化学療法社

切除不能大腸癌転移性肝腫瘍に対するOxaliplatin（L-OHP）およびIrinotecan（CPT-11）療法後，肝動注療法（HAI）の検討

加藤 健志 三宅 泰裕 土井 貴司 星 美奈子 開狩 洋一
大島 聡 飯島 正平 黒川 英司 吉川 宣輝*

〔*Jpn J Cancer Chemother* 35(12): 2015-2017, *November*, 2008〕

Third-Line Treatment of Intermittent Hepatic Arterial Infusion for Unresectable Liver Metastases from Colorectal Cancer: Takeshi Kato, Yasuhiro Miyake, Takashi Doi, Minako Hoshi, Yoichi Makari, Satoshi Oshima, Shouhei Iijima, Eiji Kurokawa and Nobuteru Kikkawa (*Dept. of Surgery, Minoh City Hospital*)

Summary

We report 6 cases of liver metastases from colorectal cancer with third-line treatment of intermittent hepatic arterial infusion and systemic chemotherapy for unresectable liver metastases with clinical signification of direct invasion to adjacent organs in Stage IV colorectal cancer. Subjects were 19 consecutive patients who underwent R0 surgery to the primary tumor for colorectal carcinoma, pT4, M1 in 1995-2003. We studied the relationship of pathological invasion to adjacent organs of tumor to other clinicopathological factors to prognosis. Of the 19 patients, 11 (57.8%) were R0 surgery to the tumor of metastases. Only 4 (36.7%) patients survived more than 3 years. The patient without excision did not survive for three years. The median survival time was only 8.5 months. Multivariate analysis indicated that only R0 surgery to the tumor of metastases was an independent prognostic factor. The optimum resection for adjacent organs may prolong a survival. But the extended resection is a possibility of shortening the survival time. Key words: Colorectal cancer, Hepatic arterial infusion chemotherapy, Third-line therapy

要旨 切除不能大腸癌肝転移に対する標準治療はFOLFOX，FOLFIRI療法である。それに続く三次治療として，HAI＋全身化学療法を施行した6例について検討したので報告する。6例の一次治療はmFOLFOX6 3例，FOLFIRI 2例，CPT-11＋5-DFURが1例であった。二次治療はFOLFIRI 3例，mFOLFOX6が3例であった。三次治療の奏効率は13%でPRが1例であった。その他はSD症例4例で，PDが1例であった。HAIによる有害事象はgrade 3以上の重篤なものは認めず，全例で安全に行うことが可能であった。HAI施行後PRの1例に対して切除術を施行した。予後は肺転移3例，腹膜播種1例，局所再発2例を認めた。HAI開始後のMSTは9か月で全例が原病死していた。HAIは局所制御には優れているが，肝外病巣の制御には不十分である。今後は分子標的治療薬との併用療法の開発が必要だと思われる。

はじめに

切除不能転移再発大腸癌に対する治療法は，FOLFOX療法とFOLFIRI療法の同等性が証明され[1]，一次，二次治療において標準療法として確立されたといっても過言ではない。しかし，それに続く三次治療はcetuximabやpanitumumabが承認されていない現在，治療法の選択に苦慮しているのが現状である。そこで当院では，oxaliplatin（L-OHP）およびirinotecan（CPT-11）療法後の三次治療として，切除不能肝転移症例に対し肝動注療法（HAI）を行っているので報告する。

I. 対象，方法（図1）

当院にてL-OHP承認後に治療を施行した大腸癌の肝転移症例は81例で，そのなかで切除可能と診断した症例は27例であり，今回は切除不能と診断した54例を対象とした。切除不能症例に対して一次，二次治療としてL-OHP療法およびCPT-11療法を施行した症例は33例で，その三次治療としてHAIを施行した6症例（全体の11%）について検討した。HAIはweekly high-dose 5-FU（1,000 mg/m² 5時間 day 1，7，15，22，1週休薬）にCPT-11（100 mg/m² day 1，15）またはUFT（300 mg/m² day 1～28）を行った。

連絡先：〒562-8562 箕面市萱野5-7-1 ＊箕面市立病院 胃腸センター・外科
加藤 健志

0385-0684/08/¥500/論文/JCLS

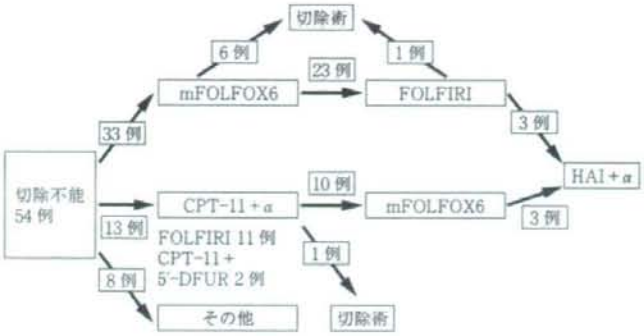


図 1 切除不能大腸癌転移性肝腫瘍に対する治療法

表 1 HAI三次治療症例

No.	性別	年齢		時期	転移個数	肝外転移	一次治療		二次治療		三次治療		予後
							コース数	効果	コース数	効果	コース数	効果	HAI開始後
1	男性	59	結腸	異時	7		CPT-11+5'-DFUR (7コース)	PR	FOLFOX (4コース)	PD	HAI+UFT (4コース)	PR	肝切除術 肺転移再発 18か月死亡
2	男性	65	直腸	同時	11	肺	CPT-11+5'-DFUR (7コース)	SD	FOLFOX (11コース+FL 6コース)	PR	HAI+CPT-11 (5コース)	SD	肺転移増大 11か月死亡
3	女性	65	直腸	同時	8		FOLFIRI (8コース)	SD	FOLFOX (6コース+FL 7コース)	SD	HAI+CPT-11 (6コース)	SD	肺転移 11か月死亡
4	男性	62	直腸	異時	4	リンパ節	FOLFOX (9コース+FL 8コース)	PR	FOLFIRI (6コース)	SD	HAI+UFT (4コース)	SD	局所再発 9か月死亡
5	男性	52	直腸	異時	7	肺	FOLFOX (2コース)	PD	FOLFIRI (4コース)	PD	HAI+UFT (5コース)	SD	局所再発 12か月死亡
6	男性	62	直腸	異時	5		FOLFOX (11コース+FL 7コース)	PR	FOLFIRI (11コース)	SD	HAI+CPT-11 (2コース)	PD	腹膜播種 3か月死亡

II. 結 果

1. 一次治療

切除不能肝転移に対して一次治療でL-OHP療法を施行した症例は33例で，CPT-11療法は13例であった。L-OHP療法は全例mFOLFOX6療法で，奏効率は57%（19/33）（CR 1例）であった。CPT-11療法はFOLFIRI療法が11例，CPT-11+5'-DFURが2例で，奏効率は46%（6/13）であった。mFOLFOX6療法後に切除術を行った症例は6例で，FOLFIRI療法後1例に切除術を施行した。

2. 二次治療

mFOLFOX6療法後の23例にFOLFIRI療法を施行し，奏効率は17%（4/23）で1例に切除術を施行した。CPT-11+α療法後にmFOLFOX6療法を10例に施行し，奏効率は20%（2/10）であった。

3. 三次治療

HAIを施行した症例は6例で，三次治療施行対象症例33例に対する13%でHAIを施行した6例を表1に示した。3例にCPT-11を，3例にUFTを併用した。3例が一次治療にmFOLFOX6療法を，3例がCPT-11+α療法を施行していた。奏効率は13%で1例にPRを認めた。その他は4例がSDで，6例中5例で肝転移巣のコントロールが可能であった。またgrade 3以上の有害事象は認めず，カテーテルトラブルも認めなかった。PRの1例に対して肝切除術を施行した。

4. 予 後

肺転移3例，腹膜播種1例，局所再発に2例を認めた。HAI開始後のMSTは9か月で，PRの症例はHAI後肝切除術を施行した。しかし，肝切除術後6か月後に肺転移を認めた。

III. 考 察

切除不能大腸癌肝転移症例に対する治療は，一次，二次治療としてFOLFOXおよびFOLFIRIにbevacizumabを併用した治療法が標準療法として確立している。切除不能大腸癌の予後はFOLFOX，FOLFIRI療法の出現により著明に延長したが，それに続く三次治療には決めてとなる治療法がなく，治療に難渋しているのが現状である。今年，cetuximabの承認が予想されているが，

それに引き続く治療法に難渋するのは現在と同様で，有効な治療法の工夫が重要である。

HAIの肝局所での腫瘍縮小効果は強く，局所制御を証明する報告は複数なされているが，生存期間を改善するとの報告は少ない[2]。

その理由は肝外転移の発現率が高率であり，生存期間を延長するには至らないからである[2]。そこで肝外転移を抑制する目的で，HAIに全身化学療法を追加する臨床研究が行われ，有効である[3]との報告もあるが，ランダム化試験の報告はない。またカテーテルによる仮性動脈瘤や血管外逸脱など重篤で特殊な合併症も認めるのが現状である[4]。さらに有効なFOLFOXやFOLFIRIなどの全身化学療法が開発された現在，HAIは転移性肝腫瘍の一次治療として行われることが少なくなった。HAI療法の三次治療における報告は少なく，FOLFOX，FOLFIRI後の報告はわれわれが調べたかぎりではない。

今回の検討では6例中1例にPRを認め，4例はSDであり，合計5例で局所制御効果を認めた。またPRの1例では化学療法後に切除が可能となり，切除術を施行している。有害事象は重篤なものを認めず，三次治療でも安全に行うことが可能であった。また定期的な血流改善とカテーテルの挿入を必要とする点を除くと，治療時間もFOLFOXやFOLFIRIと比較して短く，患者自身のQOLも高いと思われた。しかし，HAIに肝外転移を予防するために全身化学療法を追加したが，治療中に6例中5例で肝外転移を認め，有効な治療法はなく，次の治療に移ることができないのが現状であった。

今後はHAIにL-OHPや分子標的治療薬を追加した併用療法の開発が重要で，L-OHPの併用は一次治療の第I相試験結果ではあるが，90%程度の奏効率[5]であり，有望であると思われる。これにbevacizumabやcetuximabの併用療法の試験をデザインし，三次治療への応用を考慮する必要がある。

本論文の要旨は第30回日本癌局所療法研究会において発表した。

文　献

1) Tournigand C, André T, Achille E, *et al*: FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* **22**(2): 229–237, 2004.
2) 荒井保明，松枝　清，稲葉吉隆：大腸がん肝転移に対する動注化学療法．癌と化学療法 **27**(14): 2193–2200, 2000.
3) Arai Y, Inaba Y, Takeuchi Y, *et al*: Intermittent hepatic arterial infusion of high-dose 5FU on a weekly schedule for liver matastases from colorectal cancer. *Cancer Chemother Pharmacol* **40**(6): 526–530, 1997.
4) 加藤健志，吉川宣輝，山本浩嗣・他：肝動注化学療法症例における合併症の検討．癌と化学療法 **29**(12): 2125–2128, 2002.
5) Kemeny N, Jarnagin W, Paty P, *et al*: Phase I trial of systematic oxaliplatin combination chemotherapy with hepatic arterial infusion in patients with unresectable liver matastases from colorectal cancer. *J Clin Oncol* **23**(22): 4888–4896, 2005.

V．大腸癌肝転移切除後患者を対象としたフルオロウラシル/l-ロイコボリンとオキサリプラチン併用補助化学療法（mFOLFOX6） vs. 手術単独によるランダム化 II/III 相試験実施計画書 ver 1.2

JCOG
Japan Clinical Oncology Group

Japan Clinical Oncology Group（日本臨床腫瘍研究グループ）
大腸がんグループ

厚生労働省がん研究助成金指定研究 3(20 指-3) 主任研究者：島田安博(国立がんセンター中央病院)
「消化器悪性腫瘍に対する標準治療確立のための多施設共同研究」班
厚生労働省科学研究費補助金 第 3 次対がん総合戦略研究事業がん臨床研究事業 主任研究者：加藤知行(愛知県がんセンター中央病院)
「大腸がん肝転移症例の術後補助化学療法に関する研究」班

JCOG0603

大腸癌肝転移切除後患者を対象としたフルオロウラシル/l-ロイコボリンとオキサリプラチン併用補助化学療法（mFOLFOX6） vs. 手術単独によるランダム化 II/III 相試験実施計画書 ver 1.2

Randomized Study of Hepatectomy + mFOLFOX6 vs. Hepatectomy Alone for Liver Metastasis of Colorectal Cancer

略称： Adj-mFOLFOX6 PII/III

大腸がんグループ代表者
森谷 宜皓
国立がんセンター中央病院 大腸外科

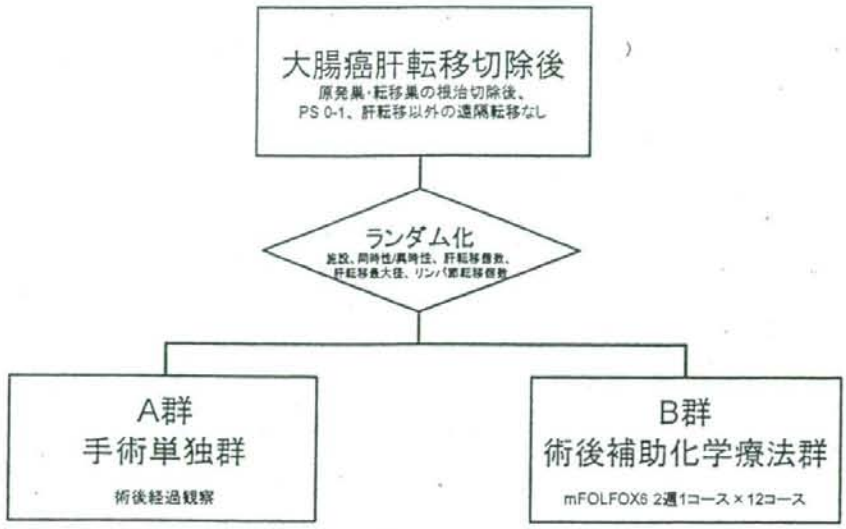
研究代表者
加藤 知行
愛知県がんセンター中央病院
〒464-8681 愛知県名古屋市千種区鹿子殿 1-1
TEL: 052-762-6111/FAX: 052-763-5233
E-mail: tkato@aichi-cc.jp

研究事務局
清水 泰博
愛知県がんセンター中央病院 消化器外科部
〒464-8681 愛知県名古屋市千種区鹿子殿 1-1
TEL:052-762-6111/FAX:052-763-5233
E-mail: yshimizu@aichi-cc.jp

コンセプト承認(PC408):	2004 年 9 月 11 日	
一次審査提出:	2006 年 6 月 23 日	
二次審査提出:	2006 年 9 月 21 日	
プロトコール承認:	2007 年 2 月 15 日	
第 1 回プロトコール改訂	2007 年 9 月 20 日承認	2007 年 9 月 27 日発効
第 2 回プロトコール改訂	2009 年 2 月 27 日承認	2009 年 3 月 9 日発効

0. 概要

0.1. シェーマ



0.2. 目的

大腸癌肝転移治癒切除後の患者を対象として、オキサリプラチン併用 5-FU/l-leucovorin 療法（mFOLFOX6）の術後補助化学療法の有用性を、標準治療である肝転移切除単独療法とのランダム化第 II/III 相試験にて検証する。

Primary endpoint：第 III 相部分：無病生存期間、第 II 相部分：9 コース完遂割合
Secondary endpoints：第 II・III 相部分共通：全生存期間、有害事象、再発形式

0.3. 対象

1）肝転移が組織学的に大腸癌と診断されている。
2）原発巣と肝転移に対して治癒切除が行われている。
3）肝臓以外の遠隔転移・再発を認めない。
4）以下の i)～ii）以外の化学療法（肝動注を含む）の既往がない。
　i）抗がん剤最終投与日から 3 か月以上経過した術後補助化学療法（オキサリプラチンを除く）
　ii）直腸癌に対する 3 か月以上経過した化学放射線療法もしくは放射線単独療法（オキサリプラチンを除く）
5）肝転移に対して、ラジオ波焼灼術などの熱凝固療法や凍結療法の既往がない。
6）肝転移切除後、42～70 日である。
7）年齢が 20 歳以上 75 歳以下である。
8）PS（ECOG）が 0、1 である。
9）臓器機能が保たれている。
10）試験参加について、患者本人から文書で同意が得られている。

0.4. 治療

A 群：手術単独群
　再発が認められるまで無治療で経過観察を行う。
B 群：術後補助化学療法群
　mFOLFOX6 療法を 2 週 1 コースとして 12 コース繰り返す。
　mFOLFOX6 療法：以下の①→②→③の順で行う。

①	Oxaliplatin: 85 mg/m² + l-leucovorin: 200 mg/m²	静注（2hrs）	day1
②	5-FU: 400 mg/m²	急速静注	day1
③	5-FU: 2,400 mg/m²	持続静注(46hrs)	day1～3

0.5. **予定登録数と研究期間**

予定登録数:300 名。

第 II 相部分:78 名　　登録期間:1 年。追跡期間:第 II 相部分登録終了後 7 ヶ月

第 III 相部分:300 名(II 相部分含む)　　登録期間:3 年。追跡期間:登録終了後 5 年。総研究期間:8 年

0.6. **問い合わせ先**

適格規準など、臨床的判断を要するもの:研究事務局(表紙、16.6.研究事務局)

化学療法、治療変更規準など、臨床的判断を要するもの:化学療法研究事務局(16.7.化学療法研究事務局.)

登録手順、記録用紙(CRF)記入など:JCOG データセンター(16.12.)

有害事象報告:JCOG 効果・安全性評価委員会事務局(16.10.)

目次