

INTRODUCTION

Gastric cancer remains a major cause of death in Asian countries, and this tumor type is the second leading mortality cause in Japan. The majority of gastric cancer cases are diagnosed at an unresectable stage at which the prognosis is extremely poor. Current treatment for unresectable gastric cancer is based on systemic chemotherapy with an oral fluoropyrimidine (i.e. S-1 or capecitabine) plus cisplatin. S-1 plus cisplatin is a standard treatment in Japan based on the SPIRITS trial, which demonstrated the superiority of S-1 plus cisplatin compared with S-1 alone, while capecitabine plus cisplatin has also been recognized as a standard therapy around the world (1,2).

Patients exhibit peritoneal metastasis in approximately half of all cases of unresectable gastric cancer. Peritoneal metastasis causes many serious complications, such as malignant ascites, intestinal obstruction, hydronephrosis and obstructive jaundice. Gastric cancer patients with severe peritoneal metastasis, and particularly those with massive ascites, have been excluded from clinical trials of cisplatin-containing regimens, and patients with inadequate oral intake have been excluded from trials with oral fluoropyrimidine. For such patients, continuous infusion of fluorouracil (5-FU ci) had been used in Japan based on the results of a Japan Clinical Oncology Group (JCOG) 0106 trial, which demonstrated that methotrexate (MTX) and 5-FU sequential therapy (MTX/5-FU) were not superior to 5-FU ci in chemotherapy-naïve patients with peritoneal metastasis, except in those with massive ascites (3). In a recent a Phase III trial (ISO-5FU study), a weekly bolus regimen of 5-FU/*l*-leucovorin (*l*-LV) for unresectable gastric cancer was shown to be non-inferior to S-1, which had been also proved to be non-inferior to 5-FU ci in the previous JCOG9912 trial (4,5). Therefore, bolus 5-FU/*l*-LV has been used as one of the treatment options for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake in the clinical setting.

Many patients with severe peritoneal metastasis suffer from acute clinical symptoms, such as abdominal fullness, vomiting, nausea, anorexia and abdominal pain, and show rapid progression of the disease. Chemotherapy with greater therapeutic efficacy than that of 5-FU/*l*-LV is needed as first-line treatment to promptly improve the symptoms and quality of life of patients. 5-FU/*l*-LV and paclitaxel (FLTAX) are both appropriate regimens for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, because this regimen does not require that patients be hydrated and includes no oral agents. Weekly administration of FLTAX was demonstrated to be an effective regimen in Phase I/II studies for general unresectable gastric cancer patients, except those with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake (6,7). We conducted a multicenter feasibility study of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. The study consisted of two

phases: in the first phase, we assessed the dose-limiting toxicity (DLT) and determined the maximum tolerated dose (MTD) and recommended dose (RD), and in the second phase, the feasibility of the FLTAX regimen at the RD level was assessed in an additional group of patients.

PATIENTS AND METHODS

ELIGIBILITY CRITERIA

Eligibility criteria included: histologically proven gastric adenocarcinoma; unresectable advanced or recurrent disease; age range of 20–80 years; Eastern Cooperative Oncology Group performance status of 0–2; peritoneal metastasis with bowel stenosis confirmed by barium enema, ascites and/or peritoneal nodule detected by computed tomography scan; massive ascites extending throughout the entire abdominal cavity, or inadequate oral intake which is defined as receiving an intravenous drip infusion because of nutritional support or proper hydration; previously untreated disease or the disease after one prior systemic chemotherapy as follows: recurrence during adjuvant chemotherapy or within 6 months after its completion, or failure of 5-FU ci or oral fluoropyrimidine as the first-line chemotherapy; preserved organ function, including leukocyte counts $\geq 3000/\text{mm}^3$, platelet counts $\geq 100\,000/\text{mm}^3$, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 100\text{ U/l}$, total bilirubin $\leq 1.5\text{ mg/dl}$ and serum creatinine $\leq 2.0\text{ mg/dl}$ and provision of written informed consent.

The levels of ascites were classified as follows: massive ascites was defined as extending throughout the entire abdominal cavity; moderate ascites was defined as inconsistent with either mild or massive ascites; mild ascites was defined as localized only in the upper or lower part of the abdominal cavity; no ascites was defined as undetectable by computed tomography scanning.

Exclusion criteria included active infection, uncontrolled heart disease, uncontrolled diabetes, pulmonary fibrosis or active pneumonitis, history of hypersensitivity to alcohol, prior taxane-containing chemotherapy, massive pleural effusion, symptomatic brain metastasis, watery diarrhea, active concomitant malignancy and pregnancy or lactation.

This study was approved by the independent ethics committee for each trial center and was conducted in accordance with the Declaration of Helsinki, and local laws and regulations. This study was registered with UMIN-CTR, number 000002093.

STUDY DESIGN AND TREATMENT

This was a multicenter feasibility study conducted in 2 phases, carried out across 12 sites in Japan. The first phase consisted of a dose-escalation study to determine DLT, MTD and RD of FLTAX. The predefined dose escalation scheme in the first phase consisted of two levels as follows: Level 1, 500 mg/m² of 5-FU, 250 mg/m² of *l*-LV and

60 mg/m² of paclitaxel; Level 2, 600 mg/m² of 5-FU, 250 mg/m² of *l*-LV and 80 mg/m² of paclitaxel.

In the first phase, six patients were enrolled per dose level. If 0–2 DLT occurred in six patients, the next six patients were enrolled at the next dose level. If three or more DLT were observed at dose level 1, the FLTAX regimen would be deemed unfeasible for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. In the second phase, additional patients were enrolled and were assessed together with the patients at the RD level in the first phase.

Paclitaxel was administered as a 60 min intravenous infusion followed by 5-FU as a bolus intravenous infusion. A 120 min intravenous infusion of *l*-LV was started at the same time as the paclitaxel infusion; all agents were administered on Days 1, 8 and 15 every 28 days. As prophylaxis for potential paclitaxel hypersensitivity reactions, 8 mg of dexamethasone, 50 mg of ranitidine and 10 mg of chlorpheniramine were administered before the infusion of paclitaxel. Protocol treatment was defined as two cycles of FLTAX. Completion of two cycles was defined as the successful administration of FLTAX in at least four out of a total of six doses during two cycles. Post-protocol treatment was not defined, but continuation of FLTAX was recommended until disease progression or unacceptable toxicity occurred.

DOSE-LIMITING TOXICITY AND RD

A DLT was defined as any of following events observed in Cycle 1: febrile neutropenia; neutrophil counts <500/mm³ for 5 days or longer without use of granulocyte colony-stimulating factor; platelet counts <25 000/mm³ or requiring platelet transfusion; Grade 3 non-hematological toxicity except for glucose, electrolyte, nausea, vomiting, anorexia, constipation and fatigue; treatment delay of Cycle 2 longer than 14 days and skipping of chemotherapy on Days 8 and 15 in Cycle 1 and treatment delay of Cycle 2 due to prolonged toxicities.

DOSE MODIFICATION OF FLTAX

When adverse events, described as follows, developed in Cycle 1, the dosage at Cycle 2 was reduced by one level: neutrophil counts <500/mm³; febrile neutropenia; infection with Grade 3 or 4 neutropenia; platelet counts <25 000/mm³; Grade 3 or higher non-hematological toxicity except for glucose, electrolyte, nausea, vomiting, anorexia, constipation and fatigue; delay of Day 1 in Cycle 2 longer than 8 days or skipping of chemotherapy on both Days 8 and 15. Dose reduction was performed level-by-level from Level 2 to Level 0: the lowest dosage (Level 0) of 400 mg/m² of 5-FU, 200 mg/m² of *l*-LV and 50 mg/m² of paclitaxel, dosage of Level 1 and Level 2 is shown in *Study design and treatment*. Once the dosage of each drug was reduced, a regain in dosage was not permitted. If Grade 3 sensory neuropathy did not recover by the start of a subsequent cycle,

treatment could be continued with 5-FU/*l*-LV alone. Dose adjustment was done on a per cycle basis but not within a cycle.

CRITERIA FOR ADMINISTRATION ON DAY 8 AND 15

When adverse events, described as follows, developed on Day 8 and 15 in each cycle, administration of FLTAX was skipped: neutrophil counts <1000/mm³, platelet counts <75000/mm³, AST or ALT >150 IU/l, total bilirubin >2.0 mg/dl, serum creatinine >2.0 mg/dl, fever (38.0°C or higher), and physician's decision due to Grade 2 or higher non-hematological toxicities.

CRITERIA FOR STARTING CYCLE 2

After confirming that the following criteria were met, Cycle 2 was started: leukocyte counts ≥3000/mm³, neutrophil counts ≥1500/mm³, platelet counts ≥100 000/mm³, serum creatinine ≤2.0 mg/dl, total bilirubin ≤2.0 mg/dl, without fever (38.0°C or higher) and recovery of non-hematological toxicities appearing in Cycle 1 to Grade 1 or lower at initiation of Cycle 2. If initiation of Cycle 2 was delayed more than 4 weeks from the scheduled initiation date, the patient was withdrawn from the study.

STUDY ASSESSMENTS

Physical examination and laboratory tests were checked every week during the protocol treatment, and adverse events were assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Tumor response was evaluated for patients with measurable lesions after each cycle during protocol treatment with the Response Evaluation Criteria in Solid Tumors guidelines, version 1.0 using computed tomography of the chest, abdomen and pelvis (8). The ascites response was evaluated as follows: complete response (CR) was defined as disappearance of ascites; partial response (PR) was defined as decreasing by one or more levels, as described above; incomplete response/stable disease was defined as other than CR, PR or progressive disease (PD) and PD was defined as an increase by one or more level, or need for more frequent drainage.

Overall survival was defined from the date of registration to the date of death or to the last contact date. Progression-free survival was defined from the date of registration to the date of disease progression or death from any cause. If there was no documented disease progression and if the patient had not died, data on progression-free survival were censored on the date that the absence of progression was confirmed.

STUDY ENDPOINTS

The primary endpoints were the RD of FLTAX based on the assessment of DLT and MTD in the first phase of the study,

and the feasibility of FLTAX in peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake based on the completion rate of two cycles in the second phase. The secondary endpoints were safety, ascites response rate, progression-free survival and overall survival.

STATISTICAL ANALYSIS

The completion rate of two cycles of FLTAX as the primary endpoint was expected to be 60% based on data from clinical trials of advanced gastric cancer patients with ascites indicating a median treatment duration of 8–10 weeks (9–11). The threshold rate of completion of two cycles was set at 30%, with an α of 0.1 (one-sided) and power of 80%, and the required number of patients was 19. The target number of patients was set at 20 to allow for a sufficiently large study cohort after dropouts and exclusions. Progression-free survival and overall survival were estimated using the Kaplan–Meier method.

RESULTS

PATIENTS

From June 2009 to July 2010, 32 patients were registered in this study: 13 patients were enrolled in the first phase—6 at Level 1, and 7 at Level 2. One patient at Level 2 was registered but never received protocol treatment and failed to meet the administration criteria over 7 days. Twenty-five patients who received the RD (including six patients at Level 1 in the first phase) were evaluated in the second phase. By the time of registration of 15 patients in the second phase, death within 30 days after the last administration of FLTAX including post-protocol treatment occurred in six patients (three second-line patients at Level 1, two second-line patients at Level 2 and one first-line patient at Level 2). All these patients died from disease progression, except one second-line patient at Level 2 who died due to a treatment-related cause. The continuation of this study was approved by the Date and Safety Monitoring Committee after protocol amendment to limit the patients in first-line setting. Table 1 shows the baseline demographics of the patients in the first and second phases.

MTD AND RD DETERMINATION

In the first phase, one of six patients at Level 1 had DLT of Grade 4 gastrointestinal perforation (a good response to chemotherapy resulted in perforated gastric cancer). Two of six patients at Level 2 had DLT (one had Grade 3 febrile neutropenia and another had Grade 3 infection of the central venous device without neutropenia), and there was one treatment-related death; a patient who developed pneumonia with Grade 4 neutropenia at 17 days after protocol treatment out of the DLT assessment period. Therefore, Level 2 was

Table 1. Patient characteristics

Category	First phase		Second phase
	Level 1 (n = 6)	Level 2 (n = 6)	RD (n = 25) ^a
Age, median (range)	63 (57–69)	49 (32–69)	65 (55–75)
Gender, male/female	5/1	3/3	15/10
ECOG PS, 0/1/2	0/4/2	0/5/1	1/19/5
Severe peritoneal metastasis			
Massive ascites	2	1	13
Inadequate oral intake	3	2	9
Massive ascites and inadequate oral intake	1	3	3
Drip infusion			
Peripheral infusion	2	0	3
IVH	2	5	9
Primary lesion			
Absent/present	1/5	1/5	5/20
Prior chemotherapy			
Absent	3	4	18
Present	3	2	7
S-1	1	0	1
S-1/CDDP	2	2	6
Histology			
Intestinal type	0	1	3
Diffuse type	5	4	21
Adenocarcinoma (only cytology)	1	1	1
Ascites			
None	0	0	1
Mild	3	2	6
Moderate	0	0	2
Massive	3	4	16

RD, recommended dose; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IVH, intravenous hyperalimentation; CDDP, cisplatin. ^aThe RD group (n = 25 patients) included six patients at Level 1 dose in the first phase.

considered as the MTD and Level 1 was determined as the RD for the second phase of the study.

FEASIBILITY AND SAFETY

The completion rate of two cycles in the second phase was 92% [90% confidence interval (CI): 76.9–98.5]: 21 of 25 patients continued further FLTAX treatment after protocol treatment of two cycles, and the median number of cycles was 4 (range 1–11). The reasons for treatment discontinuation in the second phase were disease progression (n = 21)

Table 2. Adverse events (during Cycle 1 and 2)

Category	First phase				Second phase	
	Level 1 (n = 6)		Level 2 (n = 6)		RD ^a (n = 25)	
	All grades n	Grade ≥ 3 n	All grades n	Grade ≥ 3 n	All grades n (%)	Grade ≥ 3 n (%)
Hematologic toxicities						
Neutropenia	2	1	3	3	10 (40)	3 (12)
Leucopenia	3	1	3	2	24 (96)	2 (8)
Hemoglobin	5	2	6	2	24 (96)	3 (12)
Thrombocytopenia	1	0	1	0	3 (12)	0
Non-hematologic toxicities						
Bilirubin	2	0	0	0	4 (16)	0
AST	3	0	1	0	6 (24)	0
ALT	3	0	1	0	4 (16)	0
Hyponatremia	3	3	4	1	12 (48)	4 (16)
Hypokalemia	4	3	2	0	8 (32)	3 (12)
Creatinine	2	0	2	0	7 (28)	0
Anorexia	6	4	5	2	19 (76)	4 (16)
Nausea	4	0	3	0	15 (6)	0
Vomiting	4	0	2	0	11 (44)	0
Diarrhea	3	0	3	0	9 (36)	0
Fatigue	6	2	4	0	20 (80)	2 (8)
Mucositis	1	0	2	0	4 (16)	0
Neuropathy sensory	1	0	2	0	7 (28)	0
Neuropathy motor	0	0	0	0	1 (4)	1 (4)
Allergic reaction	0	0	0	0	0	0
Febrile neutropenia	0	0	0	2	0	0
Infection	0	0	0	1	4 (16)	1 (4)

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
^aThe RD group (n = 25 patients) included six patients at Level 1 dose in the first phase.

and unacceptable toxicity (n = 4) consisting of Grade 2 sensory neuropathy (n = 2), Grade 3 motor neuropathy (n = 1) and Grade 3 perforation of the primary site (n = 1). Thirteen patients in the second phase received subsequent chemotherapy after FLTAX treatment.

Table 2 summarizes all toxicities observed during the protocol treatment. At the RD level, major Grade 3 or 4 toxicities were neutropenia, leucopenia, fatigue and anorexia.

TREATMENT EFFICACY

In the second phase, the ascites response was evaluated in 24 patients but not in 1 patient with peritoneal nodules. The overall ascites response rate was 44.0% (five patients CR, six patients PR). The ascites response rate in the 17 first-line patients in the second phase was 44.4%, and that of the 7 second-line patients in was 42.9%. At a median follow-up of

8.0 months, the median progression-free survival in the second phase was 4.2 months (Fig. 1): 6.2 months in first-line patients (n = 18) and 2.9 months in second-line patients (n = 7). Median overall survival in the second phase was 8.0 months (Fig. 2): 9.5 months in first-line patients (n = 18) and 5.6 months in second-line patients (n = 7).

DISCUSSION

Our results suggest that FLTAX is a feasible and promising regimen for first-line treatment of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. The RD was determined as 500 mg/m² of 5-FU, 250 mg/m² of *L*-LV and 60 mg/m² of paclitaxel on Days 1, 8 and 15, every 28 days. At the RD level, the toxicity profile was acceptable and the completion rate of two cycles was

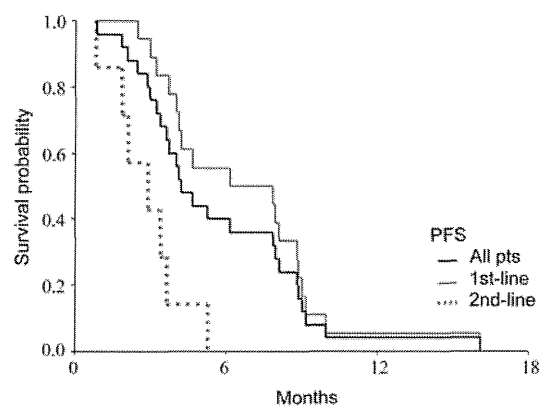


Figure 1. Progression-free survival in 25 patients at the recommended dose (RD) in the second phase of the study.

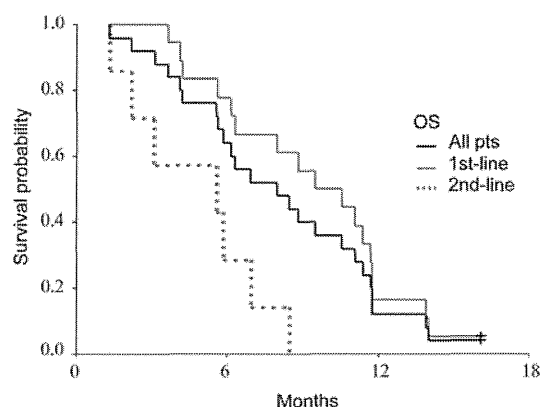


Figure 2. Overall survival in 25 patients at the RD in the second phase of the study. Tick marks indicate censored cases.

92%. Efficacy in the second phase of the study was promising; the response rate in ascites was 44%, the median progression-free survival was 4.2 months and median overall survival was 8.0 months.

Severe peritoneal metastasis causes severe clinical symptoms, such as abdominal fullness, vomiting, nausea, anorexia and abdominal pain, and it reflects rapid progression of the disease. Chemotherapy with greater therapeutic efficacy is needed as first-line treatment to promptly improve the symptoms and quality of life of patients. Furthermore, about 75% of patients with unresectable gastric cancer received second-line chemotherapy in some Phase III trials previously reported from Japan (1,5,12,13). However, only 40% of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, who received 5-FU-based regimen as first-line chemotherapy, received second-line chemotherapy in our retrospective study (14). These data revealed that many patients with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake must have missed the opportunity to receive second-line chemotherapy because of rapid progression at the failure of first-line chemotherapy. Therefore, the use of a powerful

combination regimen as first-line treatment is a promising strategy to improve the overall prognosis.

Bolus 5-FU/LV has been widely used in clinical practice for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, who cannot receive standard treatment (oral fluoropyrimidines plus cisplatin) for general unresectable gastric cancer. Weekly paclitaxel was shown to significantly improve progression-free survival (hazard ratio, 0.57; 95% CI, 0.37–0.87; $P = 0.004$) when used as a second-line treatment in patients with peritoneal metastasis, except those with massive ascites (15). Therefore, a combination regimen of FLTAX would be more effective for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake because this combination regimen does not require the patient to be hydrated and includes no oral agents. FLTAX was already demonstrated to be an effective regimen in Phase I/II studies of general unresectable gastric cancer patients (6,7) and, therefore, we sought to evaluate the feasibility of FLTAX for the treatment of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake.

The median survival time in patients with peritoneal disseminated gastric cancer and massive ascites was much longer (8.0 months) with FLTAX treatment in our study than with MTX/5-FU (5.1 months) in a previous Phase II study (9). In retrospective studies, the median survival time of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake who received systemic chemotherapy was 4.6–5.0 months (14,16). Furthermore, the ascites response rate in this study (44%) was also higher than that of MTX/5-FU (35%) in the Phase II study described above. Such high therapeutic efficacy would improve severe clinical symptoms at the start of first-line chemotherapy, and lead more patients to receive second-line chemotherapy, thereby improving the prognosis. In fact, 77% of first-line patients at the RD level could receive second-line chemotherapy, and an overall survival time of 9.5 months was achieved in this study.

In conclusion, the FLTAX regimen of FLTAX (500/250/60 mg/m²) is feasible as a first-line treatment for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. We intend to assess the FLTAX regimen relative to therapy with 5-FU/LV in a randomized trial of previously untreated patients with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake.

Acknowledgements

We are grateful to the participating patients and their families and to all other co-investigators who contributed and recruited patients for the study. We would like to thank the Clinical Trial Coordination Office (Yushi Nagai, Michiyo Tada and Asako Sakamoto) for data management and correction of CRF, and Makiko Shinogi for administrative work.

Funding

This study was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, Japan.

Conflict of interest statement

None declared.

References

1. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9:215–21.
2. Kang YK, Kang WK, Shin DB, et al. Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomized phase III noninferiority trial. *Ann Oncol* 2009;20:666–73.
3. Shirao K, Boku N, Yamada Y, et al. Randomized phase III study of 5-fluorouracil continuous infusion (5FUci) versus methotrexate and 5-FU sequential therapy (MF) in gastric cancer with peritoneal metastasis (JCOG0106). *J Clin Oncol* 2009;27:15s (Suppl; Abstr 4545).
4. Sawaki A, Yamaguchi K, Nabeya Y, et al. 5-FU/l-LV (RPMI) versus S-1 as first-line therapy in patients with advanced gastric cancer: a randomized phase III non-inferiority trial (ISO-5FU10 Study Group trial). *Eur J Cancer Suppl* 2009;7:363.
5. Boku N, Yamamoto S, Fukuda H, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol* 2009;10:1063–9.
6. Matsubara J, Shimada Y, Takashima A, et al. A phase I study of bolus 5-fluorouracil and leucovorin combined with weekly paclitaxel (FLTAX) as first-line therapy for advanced gastric cancer. *Jpn J Clin Oncol* 2008;38:540–6.
7. Matsubara J, Shimada Y, Kato K, et al. Phase II study of bolus 5-fluorouracil and leucovorin combined with weekly paclitaxel as first-line therapy for advanced gastric cancer. *Oncology* 2011;81:291–7.
8. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
9. Yamao T, Shimada Y, Shirao K, et al. Phase II study of sequential methotrexate and 5-fluorouracil chemotherapy against peritoneally disseminated gastric cancer with malignant ascites: a report from the Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group, JCOG 9603 Trial. *Jpn J Clin Oncol* 2004;34:316–22.
10. Imamoto H, Oba K, Sakamoto J, et al. Assessing clinical benefit response in the treatment of gastric malignant ascites with non-measurable lesions: a multicenter phase II trial of paclitaxel for malignant ascites secondary to advanced/recurrent gastric cancer. *Gastric Cancer* 2011;14:81–90.
11. Oh SY, Kwon HC, Lee S, et al. A phase II study of oxaliplatin with low-dose leucovorin and bolus and continuous infusion 5-fluorouracil (modified FOLFOX-4) for gastric cancer patients with malignant ascites. *Jpn J Clin Oncol* 2007;37:930–5.
12. Narahara H, Iishi H, Imamura H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). *Gastric Cancer* 2011;14:72–80.
13. Fujii M, Kim YH, Satoh T, et al. Randomized phase III study of S-1 alone versus S-1 plus docetaxel (DOC) in the treatment for advanced gastric cancer (AGC): the START trial update. *J Clin Oncol* 2011;29 (Suppl; Abstr 4016).
14. Iwasa S, Nakajima TE, Nakamura K, et al. First-line fluorouracil-based chemotherapy for patients with severe peritoneal disseminated gastric cancer. *Gastric Cancer* 2011;15:21–6.
15. Takiuchi H, Fukuda H, Boku N, et al. Randomized phase II study of best-available 5-fluorouracil (5-FU) versus weekly paclitaxel in gastric cancer (GC) with peritoneal metastasis (PM) refractory to 5-FU-containing regimens (JCOG0407). *J Clin Oncol* 2010;28:15s (Suppl; Abstr 4052).
16. Shitara K, Ito S, Sawaki A, et al. Improvement of oral intake following chemotherapy in gastric cancer patients with an inability to eat. *Oncology* 2010;79:211–8.

Background

The median overall survival (OS) was about 2 years in several pivotal phase III studies of chemotherapy for unresectable or metastatic colorectal cancer, in which combination therapy with 3 anticancer drugs (oxaliplatin or irinotecan and fluoropyrimidine) and a molecular target drug administered as a first-line treatment showed efficacy, and these therapies are considered as the standard treatment [1–3].

In several phase III clinical studies performed before the introduction of any molecular target drug, oxaliplatin or irinotecan and fluoropyrimidine combination chemotherapy as a first-line treatment were compared with the sequential chemotherapy started with fluoropyrimidine treatment followed by oxaliplatin or irinotecan as the second-line treatment, and no significant difference was noted in the median OS in any of these clinical studies [4–6]. The response rate was higher in combination chemotherapy, whereas progression-free survival (PFS) of sequential chemotherapy was comparable. Regarding adverse events, toxicity was lower in sequential than in combination chemotherapy, attracting attention.

It has been found that cure or long-term survival may be achieved when curative resection of the liver is performed after a response to chemotherapy in patients with liver metastasis alone [7]. As a therapeutic strategy, it has been proposed to select combination chemotherapy for patients requiring an active approach in whom curative resection may be possible after responding to chemotherapy, and sequential chemotherapy for patients for whom stability of the disease condition is important rather than responses and also those without a tumor-associated symptom not requiring an aggressive approach [8].

On the other hand, many colorectal cancer patients are elderly, aged 65 years or older, in whom the incidence of complications is high and many are frail patients. The incidence of adverse events, particularly neutropenia, is high in combination chemotherapy in the elderly compared to that in the non-elderly, although the efficacy is similar [9–14]. The characteristics of adverse events induced by 5 types of anticancer drug effective for colorectal cancer are as follows: the incidence of anti-epidermal growth factor receptor (EGFR) antibody preparation-induced skin toxicity is high, oxaliplatin is likely to protract peripheral sensory neuropathy, irinotecan induces diarrhea, malaise and depilation, bone marrow toxicity of oxaliplatin and irinotecan is slightly high, whereas the incidences of gastrointestinal hemorrhage/perforation and

thrombosis caused by an anti-vascular endothelial growth factor (VEGF) antibody preparation, bevacizumab, are very low, and the incidence of severe adverse events induced by fluoropyrimidine is lower than those induced by oxaliplatin and irinotecan. These characteristics suggest that the incidence of adverse events in chemotherapy combined bevacizumab with fluoropyrimidine may be lower than that in 3-drug combination therapy, making it more suitable as the first-line chemotherapy for frail patients, mainly the elderly.

The usefulness of chemotherapies combined bevacizumab with 5FU/LV or capecitabine has been shown in several clinical studies: these were administered to frail patients as a first-line treatment in the AVF2192g study [15] and as a sequential chemotherapy in the MAX study [16]. The median PFS times achieved by chemotherapy combined bevacizumab with fluoropyrimidine in these studies were 9.2 and 8.5 months, respectively, which were comparable to those achieved in pivotal phase III studies in which oxaliplatin or irinotecan was additionally combined (9.4 [1], 8.9 [2] and 9.6 months [3]).

In Japan, chemotherapy combined bevacizumab with S-1 achieved a favorable anti-tumor effect (response rate: 57%, PFS: 9.9 months) and caused low incidence of adverse events in frail patients aged 65 years or older in a phase II study (BASIC study), but the number of studies is still insufficient [17]. The efficacy and safety of chemotherapy combined bevacizumab with S-1 or 5FU/LV as a first-line for frail patients with unresectable or metastatic colorectal cancer were investigated based on the outcomes obtained at our hospital.

Subjects and Methods

Subjects

Twenty-six patients diagnosed with unresectable or metastatic colorectal cancer at our hospital between October 2007 and December 2010 in whom treatment was started as chemotherapy combined bevacizumab with S-1 or 5FU/LV [modified Roswell Park Memorial Institute (RPMI) regimen] were retrospectively investigated. They were aged 65 years or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and met one or more of the following conditions: serum albumin <3.5 g/dl, past medical history of radiation of the abdominal region or pelvic cavity, and incompatibility with oxaliplatin and irinotecan. This is the same as the eligibility criteria of the AVF2192g study [15].

Treatment Protocol

In chemotherapy combined bevacizumab with S-1, the daily dose of S-1 was set as follows based on the body surface area (BSA): 80 mg/day for BSA <1.25 m², 100 mg/day for 1.25 m² ≤ BSA <

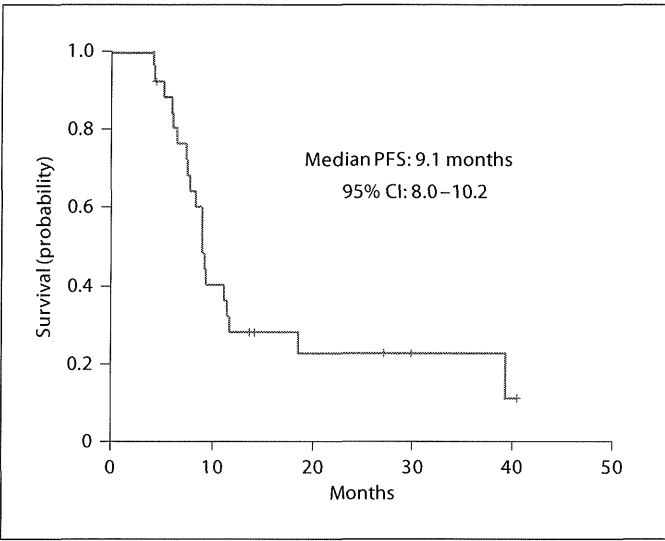


Fig. 1. Progression-free survival.

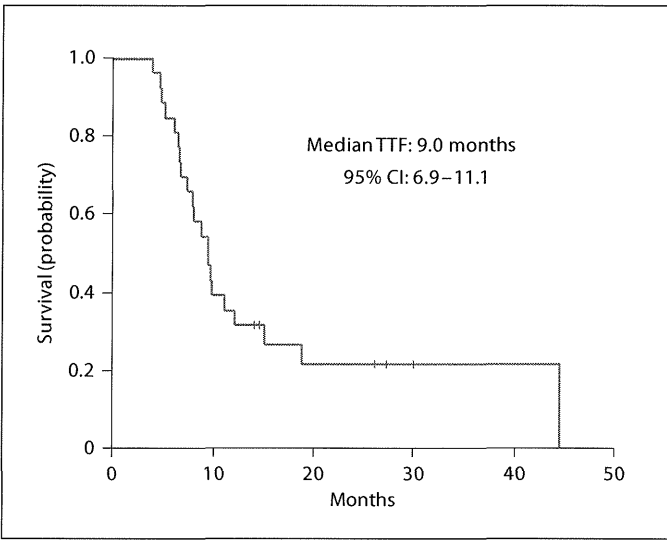


Fig. 2. Time to treatment failure.

1.5 m², and 120 mg/day for BSA ≥1.5 m². The drug was orally administered twice a day daily for 28 days, followed by a 14-day withdrawal. Bevacizumab was administered at 5 mg/kg by 30- to 90-min drip infusion on days 1, 15 and 29 (2-week intervals). One complete cycle was comprised of a total of 42 days.

In chemotherapy combined bevacizumab with 5FU/LV (modified RPMI regimen), 250 mg/m² of LV was administered by 2-hour drip infusion and 600 mg/m² of 5FU was administered by intravenous bolus injection on days 1, 8 and 15. Bevacizumab was administered at 5 mg/kg by 30- to 90-min drip infusion on days 1 and 15 (2-week interval). One complete cycle was comprised of 28 days.

Assessment of Outcome

Reponses were evaluated following the Response Evaluation Criteria in Solid Tumors version 1.0 before and after therapy in each patient. Complete response (CR) and partial response (PR) were confirmed when judged twice or more consecutively at a 4-week or longer interval.

PFS was defined as the time between the days on which consent for treatment initiation was obtained and disease progression was confirmed. When disease progression could not be confirmed, it was defined as the time until death. OS was defined as the time between the treatment initiation and death and, when death could not be confirmed, it was defined as the time until the final confirmation of survival. PFS and OS were analyzed employing the Kaplan-Meier method.

Adverse events were evaluated based on the worst grade observed during the treatment period following the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Protocol of this retrospective research approval was obtained from an institutional ethics committee at our hospital.

Table 1. Patient characteristics (n = 26)

Median age (range)	72 (66–84)
Gender (male/female)	9/17
ECOG performance status (0/1/2)	8/17/1
Primary site (colon/rectum)	14/12
Resection (yes/no)	20/6
Adjuvant chemotherapy (yes/no)	8/18
Number of metastatic site (1/2/3)	17/9/0
Metastasis	
Liver	9
Lung	9
Lymph node	11
Peritoneum	5
KRAS gene (wild/mutated/unknown)	11/7/8
S-1 + bevacizumab/5FU + bevacizumab	17/9

Results

The patient characteristics are shown in table 1. Median age was 72 years (range 66–84). ECOG performance status was 0, 1 and 2 in 8, 17 and 1 patient, respectively. The primary lesion was located in the colon in 14 patients and in the rectum in 12. Twenty patients were with resection of the primary lesion and 6 were without, 8 were with post-operative adjuvant chemotherapy and 18 were without. The number of metastasized organs was 1, 2 and 3 in 17, 9 and 0 patients, respectively. The liver, lung, lymph node and peritoneum was metastasized in 9, 9, 11 and 5 patients,

Table 2. Adverse Events by CTCAE v3.0

Event	Grade					Any grade %	Grade >3 %
	1	2	3	4	5		
Neutropenia	1	5	2	0	1	31	12
Thrombocytopenia	8	3	0	0	0	42	0
Anemia	14	5	1	0	0	77	4
Nausea	9	0	0	0	0	35	0
Diarrhea	6	2	1	0	0	35	4
Fatigue	13	0	0	0	0	50	0
Stomatitis	8	0	0	0	0	31	0
Hand-foot syndrome	10	2	0	0	0	46	0
Hypertension	3	2	3	0	0	31	12
Proteinuria	4	11	0	0	0	58	0
Epistaxis	9	0	0	0	0	35	0
Cerebral hemorrhage	0	0	1	0	0	4	4
Thrombosis	0	0	0	1	0	4	4

respectively. The KRAS gene was wild in 11, mutant in 7 and unknown in 8 patients, and treatment was chemotherapy combined bevacizumab with S-1 in 17 patients and chemotherapy combined bevacizumab with 5FU/LV in 9.

Regarding the efficacy, response was CR in 1, PR in 12, stable disease in 13, progressive disease in 0 and not evaluated 0 patients. The response rate was 50% and disease control rate was 100%. The median PFS was 9.1 months (95% CI 8.0–10.2; fig. 1). The median time to treatment failure was 9.0 months (95% CI 6.9–11.1; fig. 2), median OS was 28.9 months (95% CI 19.6–38.2) and median duration of follow-up was 20.7 months.

The mean relative dose intensity of chemotherapy combined bevacizumab with S-1 was: S-1 94.0% (range 66.5–100) and bevacizumab 62.0% (range 3.1–100), and that of with 5FU/LV was: 5FU 76.6% (range 68.6–91.3) and bevacizumab 71.7% (range 49.0–91.3).

The incidence of neutropenia at all grades was 31% and that of grade 3 or severer was 12%, the incidence of hypertension at all grades was also 31% and that of grade 3 or severer was 12%, showing low incidence, and those of other adverse events were also generally low. Grade 3 cerebral hemorrhage, grade 4 pulmonary embolus and grade 5 febrile neutropenia occurred each in 1 patient (table 2). First-line therapy was continued in 4 patients (15%), discontinuation of therapy occurred due to the following reasons: CR in 1 patient (4%), resection of liver metastasis in 1 (4%) or lung metastasis in 1 (4%), disease progression in 18 (69%) and adverse events in 3 (12%; cerebral hemorrhage, pulmonary embolus and FN). Excluding 7 patients under the first-line of therapy or course

observation, 84% of patients received second-line chemotherapy: FOLFOX/XELOX was administered to 5 patients, FOLFIRI/IRI to 9 and 5FU/LV to 2.

Discussion

We investigated the safety and efficacy of chemotherapy combined bevacizumab with fluoropyrimidine for elderly or frail patients with unresectable or metastatic colorectal cancer. The response rate was 50%, disease control rate was 100% and PFS was 9.1 months. These result suggest that such combined therapy might be useful for frail patients. However, this was a retrospective study performed at a single facility, not a prospective clinical study, and no statistical endpoint was established, showing the limitations of the study. Moreover, patient selection was biased and the OS observation period was short, indicating that the data are still immature.

Several clinical studies have reported the efficacy and safety of chemotherapy combined bevacizumab with fluoropyrimidine. In the AVF2192g randomized controlled phase II study involving frail patients, the primary endpoint, PFS, was 5.5 months in 5FU/LV therapy and 9.2 months in chemotherapy combined bevacizumab with 5FU/LV, suggesting the usefulness of combination with bevacizumab, and the therapy was tolerated with regard to safety [15]. Similarly, in the MAX study, which was a phase III study of chemotherapy combined bevacizumab with capecitabine, PFS was 5.7 months in capecitabine monotherapy and 8.5 months in chemotherapy combined bevacizumab with capecitabine, showing the usefulness of combination with bevacizumab [16]. In a phase II study of chemotherapy combined bevacizumab with capecitabine involving elderly patients, PFS was 10.8 months, suggesting high-level efficacy, and tolerability was also high [18]. In Japan, marked efficacy was also obtained in a phase II study (BASIC study) of chemotherapy combined bevacizumab with S-1 involving 65-year-old or older frail patients, in which PR was 57% and PFS was 9.9 months [17].

Regarding the efficacy, the common points of reports on chemotherapy combined bevacizumab with fluoropyrimidine are a slightly lower response rate than that of the standard combination therapy but comparable disease control rates and PFS. Based on these common findings, the standard combination therapy may be desirable for patients requiring tumor size reduction at the time of treatment initiation, but chemotherapy combined bevacizumab with fluoropyrimidine may be appropriate for patients for whom marked tumor size reduction is not nec-

essary but stabilization of the disease condition is, i.e. cases aiming at curative resection after tumor size reduction and treatment for those with no tumor-associated symptoms. It has been reported that the efficacy of combination therapy with oxaliplatin or irinotecan does not differ between elderly and young patients [9–14]. The efficacy of chemotherapy combined bevacizumab with fluoropyrimidine may also be similar in elderly and young patients because PFS in chemotherapy combined bevacizumab with capecitabine involving elderly patients in a phase II study was not markedly different from that in the MAX study, in which young patients were included [16, 18].

Regarding safety, the common points of reports on chemotherapy combined bevacizumab with fluoropyrimidine were a lower incidence of adverse events, particularly neutropenia, than that in clinical studies of the standard combination therapy, and the incidences of all grades and grade 3 or severer neutropenia were 31 and 12%, respectively [1–3]. The incidence of bone marrow toxicity, such as neutropenia, is high in combination therapies with oxaliplatin and irinotecan, particularly in elderly patients [11–16], and the induction of febrile neutropenia is of concern.

Many colorectal cancer patients are elderly, aged 65 years or older, and complications increase as patient age advances [19], meaning it can be difficult to apply chemotherapy to frail patients due to the increasing likelihood of complications. Since the patients in this study were also 65 years old or older, it included many frail patients. Regarding adverse events, the incidences of all grades and grade 3 or severer hypertension were 31 and 12%, respectively, which were higher than those in reported clinical studies. This may have been due the high age of the patients, rather than blood pressure elevation newly induced by bevacizumab.

One patient under chemotherapy combined bevacizumab with S-1 developed proteinuria in the 2nd cycle and bevacizumab administration was discontinued after day 15 in that cycle. Accordingly, the relative dose intensity of bevacizumab was 3% in this patient, but dose intensity of bevacizumab in chemotherapy combined bevacizumab with S-1 was high (81%) in the other 16 patients, and proteinuria in this patient was reversible. Therefore, the tolerability of the therapies was high, suggesting high-level safety. However, grade 3 cerebral hemorrhage, grade 4 pulmonary embolism and grade 5 febrile neutropenia occurred each in 1 patient. Performance status is likely to decrease earlier in elderly or frail patients than in young patients as adverse events develop, requiring treatment as early as possible in many cases. Thus, attention should be

paid to the development of adverse events. In actual clinical practice, standard combination chemotherapy was started at a dose lower than the recommended dose because of safety concerns in relatively many cases, but the efficacy of chemotherapy administered at a reduced dose has not been clarified. It is possible that the efficacy of sequential chemotherapy without dose reduction is higher than standard combination chemotherapy with dose reduction.

Although there have been fewer reports of clinical studies on the usefulness of sequential chemotherapy using molecular target drugs, there was no significant difference in OS between sequential chemotherapy started with fluoropyrimidine monotherapy as the first-line treatment followed by oxaliplatin or irinotecan as the second-line or later treatment, and chemotherapy combined fluoropyrimidine with oxaliplatin or irinotecan as the first-line therapy in the FOCUS [4], CAIRO [5] and FFCD 2000–2005 studies [6], suggesting the usefulness of sequential chemotherapy.

In a study of chemotherapy combined fluoropyrimidine with anti-EGFR antibody involving untreated elderly patients, the response rate was 31.8% (95% CI 20.9–44.4) and PFS was 7.1 months, which is not superior to treatment with anti-EGFR antibody preparation alone, and the incidences of grade 3 or severer adverse events were high (skin toxicity 30%, hand-foot syndrome 22% and diarrhea 18.5%), showing that it is not a favorable relationship [20].

In conclusion, the first-line chemotherapy combined bevacizumab with fluoropyrimidine for unresectable or metastatic colorectal cancer frail patients in Japan was comparable to the safety and efficacy of combination therapy reported previously in Western countries. Because chemotherapy combined anti-VEGF antibody with fluoropyrimidine is lower than the other chemotherapy regimen regarding toxicity, further clinical studies may be necessary for such combined chemotherapy not only as a treatment more tolerable for frail patients than other drug therapies, but also as the first-line treatment of sequential chemotherapy.

Disclosure Statement

The author received small payments for lectures from Chugai Pharmaceutical Co. Ltd. and Taiho Pharmaceutical Co. Ltd. Grants were also provided to the Chemotherapy Center by these 2 pharmaceutical companies.

References

1 Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013–2019.

2 Cutsem EV, Köhne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, D’Haens G, Pintér T, Lim R, Bodoky G, Roh JK, Folprecht G, Ruff P, Stroh C, Tejpar S, Schlichting M, Nippgen J, Rougier P: Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–1417.

3 Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocakova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Wolf M, Gansert J: Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697–4705.

4 Seymour MT, Maughan TS, Ledermann JA, Topham C, James R, Gwyther SJ, Smith DB, Shepherd S, Maraveyas A, Ferry DR, Meade AM, Thompson L, Griffiths GO, Parmar MK, Stephens RJ, et al: Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial. *Lancet* 2007;370:143–152.

5 Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FL, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveld OJ, van Bochove A, Sinnige HA, Creemers GJ, Tesselaar ME, Slee PH, Werter MJ, Mol L, Dalesio O, Punt CJ: Sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomized controlled trial. *Lancet* 2007;370:135–142.

6 Ducreux M, Malka D, Mendiboure J, Etienne PL, Texereau P, Auby D, Rougier P, Gasmi M, Castaing M, Abbas M, Michel P, Gargot D, Azzedine A, Lombard-Bohas C, Geoffroy P, Denis B, Pignon JP, Bedenne L, Bouché O, Fédération Francophone de Cancérologie Digestive (FFCD) 2000–05 Collaborative Group: Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2011;12:1032–1044.

7 Adam R, Wicherts DA, de Haas RJ, Ciacio O, Lévi F, Paule B, Ducreux M, Azoulay D, Bismuth H, Castaing D: Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 2009;27:1829–1835.

8 Cutsem EV, Nordlinger B, Cervantes A, ESMO Guidelines Working Group: Advanced colorectal cancer: ESMO clinical practice guidelines for treatment. *Ann Oncol* 2010;21(suppl 5):v93–v97.

9 Figer A, Perez-Staub N, Carola E, Tournigand C, Lledo G, Flesch M, Barcelo R, Cervantes A, André T, Colin P, Louvet C, de Gramont A: FOLFOX in patients aged between 76 and 80 years with metastatic colorectal cancer: an exploratory cohort of the OPTIMOX1 study. *Cancer* 2007;110:2666–2671.

10 Tournigand C, Cervantes A, Figer A, Lledo G, Flesch M, Buyse M, Mineur L, Carola E, Etienne PL, Rivera F, Chirivella I, Perez-Staub N, Louvet C, André T, Tabah-Fisch I, de Gramont A: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer – a GERCOR study. *J Clin Oncol* 2006;24:394–400.

11 Jackson NA, Barrueco J, Soufi-Mahjoubi R, Marshall J, Mitchell E, Zhang X, Meyerhardt J: Comparing safety and efficacy of first-line irinotecan/fluoropyrimidine combinations in elderly versus nonelderly patients with metastatic colorectal cancer. *Cancer* 2009;115:2617–2629.

12 Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–2342.

13 Kabbinavar FF, Hambleton J, Mass RD, Hurwitz HI, Bergsland E, Sarkar S: Combined analysis of efficacy: the addition of Bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol* 2005;23:3706–3712.

14 Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, Koski S, Lichinitser M, Yang TS, Rivera F, Couture F, Sirzén F, Cassidy J: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013–2019.

15 Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, Mass R, Perrou B, Nelson B, Novotny WF: Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol* 2005;23:3697–3705.

16 Tebbutt NC, Wilson K, Gebiski VJ, Cummins MM, Zannino D, van Hazel GA, Robinson B, Broad A, Ganju V, Ackland SP, Forgeson G, Cunningham D, Saunders MP, Stockler MR, Chua Y, Zalberg JR, Simes RJ, Price TJ: Capecitabine, bevacizumab and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX study. *J Clin Oncol* 2010;28:3191–3198.

17 Takahari D, Takiuchi H, Muro K, Tsuji A, Hamamoto Y, Yoshino T, Yoshida K, Shirao K, Miyata Y, Ohtsu A: Phase II trial of combination therapy with bevacizumab and S-1 in elderly patients with unresectable or recurrent colorectal cancer (BASIC). *Eur J Cancer Abstract Book* 2011(abstr 6121):428–429.

18 Feliu J, Safont MJ, Salud A, Losa F, García-Girón C, Bosch C, Escudero P, López R, Madoñal C, Bolaños M, Gil M, Llombart A, Castro-Carpeño J, González-Barón M: Capecitabine and bevacizumab as first-line treatment in elderly patients with metastatic colorectal cancer. *Br J Cancer* 2010;102:1468–1473.

19 Yancik R, Wesley MN, Ries LA, Havlik RJ, Long S, Edwards BK, Yates JW: Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients: population-based study. *Cancer* 1998;82:2123–2134.

20 Sastre J, Grávalos C, Rivera F, Massuti B, Valladares-Ayerbes M, Marcuello E, Manzano JL, Benavides M, Hidalgo M, Díaz-Rubio E, Aranda E: First-line cetuximab plus capecitabine in elderly patients with advanced colorectal cancer: clinical outcome and subgroup analysis according to KRAS status from a Spanish TTD group study. *Oncologist* 2012;17:339–345.

Multicenter phase II study of modified FOLFOX6 as neoadjuvant chemotherapy for patients with unresectable liver-only metastases from colorectal cancer in Japan: ROOF study

Takao Takahashi · Yoshihisa Shibata · Yuichiro Tojima · Kenji Tsuboi · Eiji Sakamoto · Katsuyuki Kunieda · Hiroshi Matsuoka · Kazuyoshi Suzumura · Mikinori Sato · Tatsushi Naganuma · Junichi Sakamoto · Satoshi Morita · Ken Kondo

Received: 17 October 2011 / Accepted: 19 January 2012
© Japan Society of Clinical Oncology 2012

Abstract

Background Neoadjuvant chemotherapy for unresectable colorectal liver metastases can reduce tumor size, which sometimes leads to curative resection. The aim of the present study was to identify and describe patients with initially unresectable liver-only metastases from colorectal cancer who obtained sufficient chemotherapeutic benefit that eventually lead to the removal of the metastatic diseases in the liver.

Methods A phase II multicenter cooperative study was conducted in 38 medical institutions using modified FOLFOX6 (mFOLFOX6) as neoadjuvant chemotherapy from

January 2008 to June 2009. Patients with liver-only metastases from colorectal cancer that was deemed not optimally resectable by liver surgeons received mFOLFOX6 as preoperative neoadjuvant chemotherapy for 6–8 cycles. Patients were reassessed for resectability after 6 cycles of mFOLFOX6. Surgery was carried out 3–6 weeks after chemotherapy. The primary endpoint was the rate of macroscopic curative surgery including liver resection.

Results 36 patients (23 male/13 female, ECOG performance status 0–1) were enrolled. The median age of the patients was 62.5 years; 78% (28 patients) had 5 or more metastatic tumors, and 50% (18 patients) had metastatic tumors over 5 cm diameter. The mFOLFOX6 regimen was

T. Takahashi (✉)
Department of Surgical Oncology, Gifu University School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan
e-mail: takaota@gifu-u.ac.jp

Y. Shibata
Department of Surgery, Toyohashi Municipal Hospital, Toyohashi, Japan

Y. Tojima
Department of Surgery, Chukyo Hospital, Nagoya, Japan

K. Tsuboi
Department of Surgery, Tosei General Hospital, Seto, Japan

E. Sakamoto
Department of Surgery, Nagoya Daini Red Cross Hospital, Nagoya, Japan

K. Kunieda
Department of Surgery, Gifu Prefectural General Medical Center, Gifu, Japan

H. Matsuoka
Department of Surgery, Fujita Health University, Toyoake, Japan

K. Suzumura
Department of Surgery, Aichi Medical University, Nagakute, Japan

M. Sato
Department of Gastroenterological Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

T. Naganuma
Department of Surgery, Saiseikai Matsusaka General Hospital, Matsusaka, Japan

J. Sakamoto
Young Leaders' Program in Healthcare Administration, Department of Social Life Science, Nagoya University, Graduate School of Medicine, Nagoya, Japan

S. Morita
Department of Biostatistics and Epidemiology, Yokohama City University School of Medicine and University Medical Center, Yokohama, Japan

K. Kondo
Department of Surgery, Nagoya Medical Center, Nagoya, Japan

safety administered resulting in 18 partial responses (50%), 12 stable disease, and 4 progressive disease. There was no grade 3/4 neurotoxicity. Fourteen patients (38.9%) underwent surgery (R0: 13; R1: 1). Of these, thirteen patients (36.1%) underwent R0 surgery.

Conclusions Our data suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a proportion of patients initially not judged to be optimally resectable.

Keywords ROOF study · mFOLFOX6 · Colorectal cancer · Unresectable liver-only metastases · Liver resection

Introduction

Colorectal cancer represents one of the most common cancers in Japan, and the liver is the most common site of metastases in patients with colorectal cancer. Liver metastases are a major cause of morbidity and mortality in this patient population. With the best supportive care, patients with liver metastases from colorectal cancer have a median survival time of 5–12 months [1–3]. Surgical resection of colorectal liver metastases is a potentially curative option, with a reported 5-year survival rate of 28–39% [4, 5]. However, about 80% of patients with colorectal liver metastases have unresectable diseases at the time of diagnosis, and long-term survival is not usually possible.

Historically, most of the patients with unresectable colorectal liver metastases have received palliative chemotherapy. However, a number of retrospective studies have reported the downsizing of colorectal liver metastases for rescue surgery following treatment with a combination of fluorouracil with irinotecan or with oxaliplatin, with the resection rate of 12.5–28% and 5-year survival rate of 33–50% after successful surgical resection [6, 7]. Resection of liver metastases can result in long-term survival in a subset of patients. A 5-year survival rate of 25–37% has been reported in a number of studies, with a median survival time of 24–42 months [8]. The improved efficacy of neoadjuvant chemotherapy has not only improved patient survival in a palliative setting, but has also offered a possibility of curative resection to previously unresectable patients with subsequent liver surgery after tumor downstaging by the chemotherapy. Adam et al. reported that liver resection could offer a possibility of long-term survival to patients with primarily unresectable metastases that were downstaged by chemotherapy. The survival rate was 33% at 5 years and 22% at 10 years, with a median survival of 39 months [5]. The use of neoadjuvant

chemotherapy in patients with initially unresectable liver metastases has been explored in a prior study. Bismuth et al. [9] reported retrospectively on the potential for surgical resection in a group of patients receiving neoadjuvant chemotherapy with oxaliplatin, fluorouracil (5-FU), and leucovorin. The addition of oxaliplatin and irinotecan to 5FU in metastatic colorectal cancer (mCRC) has improved patient survival and the chance of downsizing initially unresectable mCRC, to allow curative-intent surgery. Albert et al. [10] reported a phase II study of FOLFOX4 in a group of patients with initially unresectable liver-only metastases from colorectal cancers through the North Central Center Treatment Group (NCCTG). Seventeen out of 42 patients (40%) underwent surgery after a median of 6 months of chemotherapy.

The aim of the present study was to identify and describe patients enrolled in this trial with initially unresectable liver-only metastases from colorectal cancer, who obtained sufficient chemotherapeutic benefit that eventually led to the removal of the metastatic diseases in the liver. This study was a phase II clinical trial of mFOLFOX6 in a group of patients with initially unresectable liver-only metastases from colorectal cancer. The primary endpoint of this study was to evaluate the resection rate of the patients who had been diagnosed with unresectable colorectal cancer metastasis, who turned out to be resectable after treatment with mFOLFOX6. Secondary endpoints included (1) R0 resection rate, (2) overall survival, (3) response rate to neoadjuvant chemotherapy, (4) percentage reduction of the tumor size after chemotherapy, (5) pathological response rate, (6) adverse event of neoadjuvant chemotherapy, (7) liver damage after mFOLFOX6 treatment and safety of hepatectomy after mFOLFOX6 neoadjuvant chemotherapy.

Patients and methods

Patient selection

Patients with liver-only metastases from colorectal cancer deemed unresectable by surgeons who were experienced in liver surgery were considered as potential candidates for the study. Unresectable liver metastases was defined as (1) ≥ 5 metastatic tumors and/or (2) a tumor > 5 cm in maximum diameter or technically unresectable (inadequate future liver remnant even after surgery), such as tumors adjacent to major vascular structures that would preclude resection with tumor-free margins. At the time of study entry, patients were required to have imaging of the liver with computed tomography or magnetic resonance imaging, no evidence of extrahepatic disease and no previous history of chemotherapy with oxaliplatin or irinotecan. To

be eligible for enrolment, patients had to be aged between 20 and 75 years old, have histologically proven mCRC, adequate organ function (AST, ALT $\leq 3\times$ upper limit of normal, bilirubin $\leq 2\times$ upper limit of normal, and creatinine ≤ 1.2 mg/dl), adequate bone marrow function, and an Eastern Cooperative Oncology Group performance status of 0–1. Patients were excluded from study entry if they had received prior therapy such as hepatectomy, radiotherapy, or MCT/RFA for liver metastases. A signed written informed consent was obtained from all patients before initiating therapy. Women who were pregnant or breast-feeding were also excluded from participation to the study. This trial was approved by the medical ethics committees of all participating institutions.

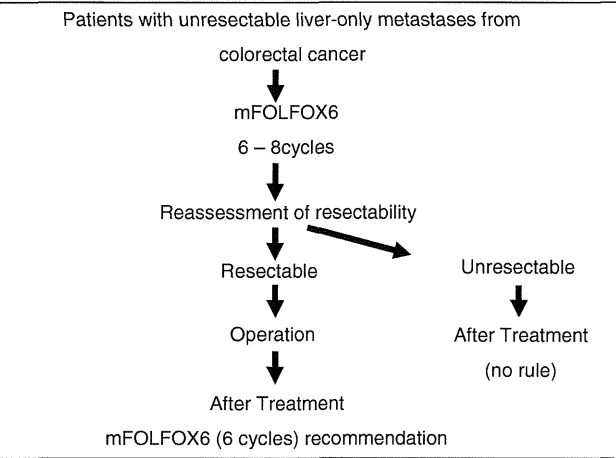
Neoadjuvant chemotherapy

Patients received mFOLFOX6, which consisted of biweekly oxaliplatin 85 mg/m², followed sequentially by leucovorin 400 mg/m², bolus 5FU 400 mg/m², and then continuous-infusion 5FU 2400 mg/m² over 46 h for 6–8 cycles.

Disease evaluation

Table 1 shows the profile of the Resection of metastatic colorectal cancer after Oxaliplatin, Fluorouracil, and leucovorin (ROOF) study. Patients with unresectable liver-only metastases from colorectal cancer were treated with 6–8 cycles of mFOLFOX6 as neoadjuvant chemotherapy. Tumor response was assessed every three cycles (6 weeks) with the same method as baseline, and was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Treatment was planned for 6–8 cycles.

Table 1 The outline of the ROOF study of patients with unresectable liver-only metastases from colorectal cancer



Reassessments for resectability after neoadjuvant chemotherapy were made. Hepatic resection was attempted by investigators when technically positive and when potentially curative. If it was judged that the tumor turned out to be resectable when it had initially been determined unresectable, tumor resection was planned within 3–6 weeks from the last administration of preoperative chemotherapy. Six cycles of mFOLFOX6 as adjuvant postoperative chemotherapy is recommended after hepatectomy.

Endpoints

The primary endpoint was the rate of patients with macroscopically curative surgery including liver resection. The definition of the patients who completed the treatment was those with unresectable liver-only metastases from colorectal cancer who were able to be treated with 6–8 cycles of mFOLFOX6 as neoadjuvant chemotherapy, with macroscopic R0 hepatectomy performed within 3–6 weeks of the last treatment cycles. If the excision of all the metastases was not possible, it was assumed that RFA or MCT in addition to hepatectomy was acceptable as the complete treatment.

Secondary endpoints included R0 resection rate, overall survival, response rate of neoadjuvant chemotherapy, percentage reduction after chemotherapy, pathological response rate, adverse event of neoadjuvant chemotherapy, and liver damage after mFOLFOX6 treatment and safety of hepatectomy.

Statistical considerations

The sample size was calculated to be 32 in order to show an improvement in resection rate from 20 to 40% with the acceptance of a 5% type I error under a 80% statistical power. Taking ineligible patients into account, the sample size in this study was set at 35.

Results

Patients characteristics

A phase II multicenter cooperative study was conducted in 38 medical institutions using mFOLFOX6 as neoadjuvant chemotherapy from January 2008 to June 2009. 36 patients (23M/13F, ECOG PS 0-1) were enrolled. Eligible patient characteristics at the time of study entry are listed in Table 2. The median age of the patients was 62.5 years, 78% (28 patients) had 5 or more metastatic tumors, and 56% (20 patients) had metastatic tumors over 5 cm in diameter. In these cases, 15 patients (42%) had ≥ 5

metastatic tumors and at least one tumor >5 cm in maximum diameter (H3) [11]. Moreover, 3 cases with liver metastases that were technically unresectable, with <5 metastatic tumors and a tumor <5 cm in maximum diameter (H1) [11], were noted (Table 2). H1, H2, and H3 of liver metastases are defined as in General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009, by Japanese Society for Cancer of the Colon and Rectum [11]. The synchronicity of liver metastases was 32 synchronous (89%) and 4 metachronous (11%).

Neoadjuvant treatment administration and adverse events

Thirty-one patients (86.1%) out of 36 enrolled patients completed treatment with 6–8 cycles of mFOLFOX6, with a median of 6 cycles of treatment (range 1–8 cycles).

For safety assessment, adverse events were graded according to National Cancer Institute Common Criteria version 2.0. With regard to the hematological toxicity, neutropenia was observed as grade 3 in 8 patients, and grade 4 in 3 patients (Table 3). As for non-hematological toxicity, there were 4 patients with grade 2 peripheral neuropathy. Grade 3/4 adverse events included nausea, vomiting, and stomatitis; there was one case (3%) with grade 3 (Table 3). No patient died from the mFOLFOX6 treatment. Six to eight cycles of mFOLFOX6 as neoadjuvant chemotherapy were administered safely in general.

Table 2 Patient characteristics

Characteristic	Cases	%
Age (years), median (range)	62.5 (45–72)	
Sex		
Male	23	64
Female	13	36
ECOG		
PS 0	35	97
PS 1	1	3
Primary tumour site		
Colon	18	50
Rectum	18	50
Reason for unresectability		
≥5 metastases	28	78
>5 cm	20	56
Technically non-resectable	3	8
Before treatment		
Operation	28	78
No operation	8	22
Synchronicity of liver metastases		
Synchronous	32	89
Metachronous	4	11

There was only one case (7%) of perioperative complications, with MRSA infection, among 14 hepatectomies.

Best response of neoadjuvant chemotherapy

The mFOLFOX6 regimen was safely administered, resulting in 18 partial responses (50%), 12 stable disease, and 4 progressive disease (Table 4). A high disease control rate of 83.3% (30/36) was also confirmed by this study.

Resection rate

14 out of 36 patients (38.9%) underwent surgery with curative intent, in whom R0 resection was achieved in 13 out of 14 patients (R0: 13; R1: 1). Thirteen patients (36.1%) underwent R0 surgery after all. Of 36 patients enrolled with unresectable liver-only metastases from colorectal cancer, the number of patients who could be treated with 6–8 cycles of mFOLFOX6 treatment was 31 (86.1%). Five cases dropped out from the treatment in 1–5

Table 3 Toxicity

No. of patients (n = 36)					
NCI-CTC grade:	1	2	3	4	3/4 (%)
Hematotoxicity					
Leukopenia	7	9	3	0	8
Neutropenia	2	4	8	3	31
Thrombopenia	20	5	0	0	0
Anemia	19	7	1	0	3
Non-hematotoxicity					
Peripheral neuropathy	16	4	0	0	0
Nausea	9	4	1	0	3
Vomiting	1	0	1	0	3
Diarrhea	4	1	0	0	0
Appetite loss	4	0	0	0	0
Fatigue	2	0	0	0	0
Fever	2	1	0	0	0
Stomatitis	3	2	1	0	3
Dysgeusia	3	1	0	0	0

Table 4 Best response to neoadjuvant chemotherapy

	Cases (n = 36)	%
Complete response	0	0
Partial response	18	50.0
Stable disease	12	33.3
Progressive disease	4	11.1
Not evaluable	2	5.6

cycles, although it was a study protocol that six cycles or more of chemotherapy were received. Those cases with poor compliance were not able to undergo hepatectomy.

Characteristics of patients undergoing hepatectomy

Fourteen patients (11 male/3 female, ECOG performance status 0) underwent attempted post-chemotherapeutic resection of liver-only unresectable metastases from colorectal cancer. The median age of the patients was 65.2 years; the synchronicity of liver metastases were 11 synchronous and 3 metachronous. H1, H2, and H3 degrees of liver metastases occurred in one case, 10 cases, and 3 cases, respectively [11]. The median number of cycles of neoadjuvant chemotherapy was 6.5.

There were 9 cases who underwent hepatectomy among 15 cases who had received six cycles of mFOLFOX6. All 3 cases who received seven cycles of mFOLFOX6 underwent hepatectomy. However, there were only 2 cases who became eligible for hepatectomy among 12 cases who had received up to eight cycles of mFOLFOX6. According to the protocol treatment of 8 cycles of mFOLFOX6, only one case was able to undergo hepatectomy after additional mFOLFOX6. Though the standard in the protocol by which the operation is performed was after 3 weeks and within 6 weeks from the final chemotherapy, there were four cases (29%) who actually underwent hepatectomy after 7 weeks due to convenience for the patient and the hospital or problems with liver function.

Surgical procedures were partial hepatectomy in 3 patients, hepatic segmentectomy in 2 patients, hepatic lobectomy in 2 patients, hepatic segmentectomy plus partial hepatectomy in 2 patients, hepatic lobectomy plus partial hepatectomy in 2 patients, hepatic extended lobectomy plus partial hepatectomy in 2 patients, and one hepatectomy including RFA.

Degree of liver metastasis (H factor)

General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009, by Japanese Society for Cancer of the Colon and Rectum indicates an H factor regarding liver metastases [11]. H1 is defined as less than 4 liver metastases and below 5 cm in maximum diameter of liver metastases. On the other hand, H3 is defined as more than 5 liver metastases and over 5 cm in maximum diameter of liver metastases. H2 is defined as anything except H1 and H3. The response rates of H1, H2, and H3 were 66.7% (2 out of 3 H1 cases), 55.6% (10 out of 18 H2 cases), and 40.0% (6 out of 15 H3 cases), respectively. In all cases, the response rate was relatively high. There was no significant difference in response rate according to the H factor. There was only one

case (33.3%) who underwent hepatectomy among the three H1 cases of patients who could not technically have liver metastases resected. There were ten cases (55.6%) who underwent hepatectomy among 18 H2 cases with marginally unresectable liver metastases. There were three cases (20.0%) who underwent hepatectomy among 15 H3 cases. The rate of hepatectomy was the highest in H2. We were able to perform hepatectomy in one H1 case out of two with successful chemotherapy, and in seven H2 cases out of ten with successful chemotherapy. Even though there were six H3 cases with successful chemotherapy, we could perform hepatectomy in only one case. In other words, it is difficult to perform hepatectomy even if chemotherapy is successful in H3 cases.

Discussion

Colorectal cancer is the third leading cause of cancer death, primarily attributed to metastatic disease rather than to the primary tumor in Japan. Surgery remains the only potentially curative treatment for metastatic disease. Less than 15% of patients with metastatic involvement are candidates for surgery. Some studies have continued to report good overall survival for patients undergoing surgical resection of their liver-only metastases from colorectal cancer [4, 12]. Chemotherapy as a first-line treatment for metastatic colorectal cancer has greatly improved within the last decade. In recent years, the survival of patients with advanced colorectal cancer has been improved, initially by the use of oxaliplatin- or irinotecan-based combination chemotherapy. Subsequently, it has been shown that the efficacy of cytotoxic chemotherapy can be enhanced by the addition of novel targeted agents, notably the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab and the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab.

Chemotherapeutic agents developed in colorectal cancer treatment, such as oxaliplatin associated with 5FU/LV, have demonstrated the ability to reduce tumor burden such that an important fraction of patients initially judged to be inoperable can be resected with curative intent [5, 12]. Delaunoy et al. [13] reported that post-chemotherapy surgical management of advanced colorectal cancer resulted in a 4.1% metastatic disease resection rate, and resection of metastatic disease after chemotherapy is possible in a small but important subset of patients with metastatic colorectal cancers, particularly after receiving an oxaliplatin-based chemotherapy regimen, with encouraging overall survival and time to progression observed in these highly selected patients. Tournigand et al. [14] found similar results for the secondary surgery rate in their trial, with a significant difference between patients treated with FOLFOX6 and

FOLFIRI (22 vs. 9%, $P = 0.02$). Response rate and resection rate is better for oxaliplatin-based chemotherapy such as FOLFOX. The resection rate has also been prospectively evaluated within phase II and III trials in patients with any-site mCRC, with relative risk of 33–66% and R0 resection rates of up to 22% reported, despite the unselected population [13–19] (Table 5).

Recently, an increasing number of reports on liver resection following intensive chemotherapy in patients with initially unresectable liver metastases have been published (Table 5). Prospective evaluation of conversion chemotherapy for the patients with liver-only, primarily unresectable disease has been undertaken in the phase II setting, with response rates of 48–71% and R0 resection rate of 12–40% in these selected populations [9, 10, 12, 15, 17, 20]. Alberts et al. [10] reported that twenty-five patients (60%) had tumor reduction and seventeen patients (40%) underwent surgery after a median of 6 months of FOLFOX4 chemotherapy in colorectal cancer patients with unresectable liver-only metastases (A North Central Cancer Treatment Group Phase II Study), which is consistent

with other studies assessing the activity of FOLFOX4 as first-line therapy for liver-limited metastatic colorectal cancer [13]. The median overall survival from mCRC treated with 5-FU, oxaliplatin and irinotecan has reached over 20 months, whether given concomitantly [15] or sequentially [14], but, despite this, <5% of unresectable patients will live as long as 5 years with chemotherapy alone. In contrast, the reported 5-year survival rate of the highly selected group of patients with initial unresectable liver-only disease treated with conversion chemotherapy, then surgery, ranges from 33 to 50% [5, 6, 20, 21].

In retrospective analysis, a direct correlation between tumor response rate and resection rate has been shown in studies investigating patients with unresectable colorectal liver metastases [21]. A superior response rate has been reported with the FOLFOXIRI regimen (66 vs. 41% with FOLFIRI) which is not able to be used in the first-line setting, with a corresponding increase in R0 resection rate, reported as 36% in a subgroup of patients with liver-only metastatic disease [15]. An apparent increase in steatohepatitis and subsequently increased 90-day mortality after

Table 5 Post-chemotherapy surgical management of advanced colorectal cancer

Authors	Trial	Metastases	Regimen	<i>n</i>	Resectability rate (%)
Delaunoy et al. [13]	N9741		FOLFOX4	267	4.1
Tournigand et al. [14]	GERCOR		FOLFOX6	111	22
Tournigand et al. [14]	GERCOR		FOLFIRI	109	9.0
Falcone et al. [15]	GONO		FOLFOXIRI	122	15
Falcone et al. [15]	GONO		FOLFIRI	122	6
de Gramont et al. [16]			FOLFOX4	210	6.7
Okines et al. [17]	First BEAT		Oxaliplatin-based chemotherapy	949	16.1
Okines et al. [17]	First BEAT		Irinotecan-based chemotherapy	662	9.7
Okines et al. [17]	NO16966		FOLFOX4/XELOX + bevacizumab	699	8.4
Okines et al. [17]	NO16966		FOLFOX4/XELOX	701	6.1
Van Cutsem et al. [18]	CRYSTAL		FOLFIRI + cetuximab	599	7.0
Van Cutsem et al. [18]	CRYSTAL		FOLFIRI	599	3.7
Bokemeyer et al. [19]	OPUS		FOLFOX6 + cetuximab	169	9.8
Bokemeyer et al. [19]	OPUS		FOLFOX4	168	4.1
Bismuth et al. [9]		Liver-only metastases	Oxaliplatin-based chemotherapy	330	16
Alberts et al. [10]	NCCTG	Liver-only metastases	FOLFOX4	44	40
Adam et al. [12]		Liver-only metastases	Oxaliplatin-based chemotherapy	701	13.5
Falcone et al. [15]	GONO	Liver-only metastases	FOLFOXIRI	39	36
Falcone et al. [15]	GONO	Liver-only metastases	FOLFIRI	42	12
Okines et al. [17]	First BEAT	Liver-only metastases	Oxaliplatin-based chemotherapy	350	24.3
Okines et al. [17]	First BEAT	Liver-only metastases	Irinotecan-based chemotherapy	230	18.7
Okines et al. [17]	NO16966	Liver-only metastases	FOLFOX4/XELOX + bevacizumab	211	12.3
Okines et al. [17]	NO16966	Liver-only metastases	FOLFOX4/XELOX	207	11.8
Folprecht et al. [20]	CELIM	Liver-only metastases	FOLFOX6 + cetuximab	53	38
Folprecht et al. [20]	CELIM	Liver-only metastases	FOLFIRI + cetuximab	53	30
Our paper	ROOF	Liver-only metastases	mFOLFOX6	36	38.9

liver resection has been reported with irinotecan given before liver surgery. Oxaliplatin is also known to affect the liver, causing sinusoidal dilatation in 19% of cases in the same series [22]. It is interesting to note that in a retrospective series of 105 patients treated with oxaliplatin-based chemotherapy with or without bevacizumab, the investigators reported a lower incidence and severity of sinusoidal dilatation in patients receiving bevacizumab ($P < 0.01$) [23]. Although the choice of chemotherapy regimen may be a key to maximizing resection rate with bevacizumab combinations, the choice to be made is unclear [17].

There are fewer safety concerns with the addition of the EGFR monoclonal antibody, cetuximab, to neoadjuvant chemotherapy. The CELIM study compared two treatment arms both containing cetuximab combined with FOLFIRI or FOLFOX6. After eight cycles, in technically unresectable disease, treatment was continued for four further cycles. In that study, the response rates of FOLFIRI plus cetuximab and FOLFOX6 plus cetuximab reached 57 and 68%, respectively. R0 resection rates of FOLFIRI plus cetuximab and FOLFOX6 plus cetuximab were 30 and 38%, respectively [20].

In our prospective study, we evaluated the efficacy of a combination regimen, 6–8 cycles of mFOLFOX6, in the neoadjuvant treatment of patients with unresectable liver metastases. The present study confirmed the well-known efficacy of mFOLFOX6, with a relatively high response rate of 50% and R0 resection rate of 36.1%. Our data indicate that neoadjuvant chemotherapy is effective mainly for patients with H2, which is defined as more than 5 liver metastases or over 5 cm in maximum diameter of liver metastases considered suitable for surgery after neoadjuvant chemotherapy. The crucial endpoint of neoadjuvant treatment is the achievement of a high R0 resection rate. Strategies that result in higher response rates can lead to high R0 rates.

The optimal regimen for patients with potentially resectable diseases is yet to be defined, but a strong correlation between response to chemotherapy and subsequent resection rate has been described [6]. Therefore, the goal of current medical treatment for unresectable metastatic colorectal cancer is to improve tumor response to maximize the rates of potentially curative resection. As mentioned above, randomized studies have recently shown that the addition of cetuximab to first-line chemotherapy (FOLFOX or FOLFIRI) significantly improves efficacy in patients without activating mutations of the *KRAS* gene in their tumors [18–20]. The use of novel agents such as cetuximab may also provide additional benefit for the R0 resection rate of colorectal liver metastases. Further studies need to address the optimum neoadjuvant combination treatment for patients with initially unresectable liver metastases and standardized criteria for determining

respectability. Finally, we suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a proportion of patients initially not judged to be optimally resectable.

Acknowledgments We thank Mai Hatta for her great help. This work was supported, in part, by a Non Profit Organization Epidemiological & Clinical Research Information Network (ECRIN).

Conflict of interest No author has any conflict of interest.

References

1. Finan PJ, Marshall RJ, Cooper EH et al (1985) Factors affecting survival in patients presenting with synchronous hepatic metastases from colorectal cancer: a clinical and computer analysis. *Br J Surg* 72:373–377
2. Goslin R, Steele G, Zamcheck N et al (1982) Factors influencing survival in patients with hepatic metastases from adenocarcinoma of the colon or rectum. *Dis Colon Rectum* 25:749–754
3. Bengtsson G, Carlsson G, Hafström L et al (1981) Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 141:586–589
4. Fong Y, Fortner J, Sun RL et al (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 230:309–318
5. Adam R, Delvart V, Pascal G et al (2004) Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 240:644–657
6. Adam R, Wicherts DA, de Haas RJ et al (2009) Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J Clin Oncol* 27:1829–1835
7. Simmonds PC, Primrose JN, Colquitt JL et al (2006) Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br J Cancer* 94:982–999
8. Fong Y (1999) Surgical therapy of hepatic colorectal metastasis. *CA Cancer J Clin* 49:231–255
9. Bismuth H, Adam R, Lévi F et al (1996) Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. *Ann Surg* 224:509–520
10. Alberts SR, Horvath WL, Sternfeld WC et al (2005) Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group Phase II Study. *J Clin Oncol* 23:9243–9249
11. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009: Japanese Society for Cancer of the Colon and Rectum
12. Adam R, Avisar E, Ariche A et al (2001) Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 8:347–353
13. Delaunoy T, Alberts SR, Sargent DJ et al (2005) Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol* 16:425–429
14. 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* 15:229–237
15. Falcon A, Ricci S, Brunetti I et al (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin,

- and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 25:1670–1676
16. 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
 17. Okines A, del Puerto O, Cunningham D et al (2009) Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO 16966 trial. *Br J Cancer* 101:1033–1038
 18. Van Cutsem E, Köhne CH, Hitre E et al (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 360:1408–1417
 19. Bokemeyer C, Bondarenko I, Makhson A et al (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 27:663–671
 20. Folprecht G, Gruenberger T, Bechstein WO et al (2010) Tumour response and secondary respectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomized phase 2 trial. *Lancet Oncol* 11:38–47
 21. Folprecht G, Grothey A, Albert S et al (2005) Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumor response and resection rates. *Ann Oncol* 16:1311–1319
 22. Vauthey JN, Pawlik TM, Ribero D et al (2006) Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 24:2065–2072
 23. Ribero D, Wang H, Donadon M et al (2007) Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastasis. *Cancer* 110:2761–2767