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Jpn J Clin Oncol 2010;40(10)913–920
doi:10.1093/jjco/hyq069
Advance Access Publication 12 May 2010

Phase I/II Study of Capecitabine Plus Oxaliplatin (XELOX) Plus Bevacizumab As First-line Therapy in Japanese Patients with Metastatic Colorectal Cancer

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Received January 8, 2010; accepted April 6, 2010

Objective: The addition of bevacizumab to fluoropyrimidine-based combination chemotherapy as first-line therapy for metastatic colorectal cancer results in clinically significant improvements in patient outcome. However, clinical trials have been conducted primarily in Caucasian patients with only a small proportion of Asian patients. This Phase I/II study was designed to evaluate the efficacy and safety of XELOX (capecitabine plus oxaliplatin) plus bevacizumab in Japanese patients with metastatic colorectal cancer.

Methods: Patients with previously untreated, measurable metastatic colorectal cancer received bevacizumab 7.5 mg/kg and oxaliplatin 130 mg/m^2 on day 1, plus capecitabine 1000 mg/m^2 twice daily on days 1–14, every 3 weeks. A three-step design evaluated in: step 1, initial safety of XELOX in six patients; step 2, initial safety of XELOX plus bevacizumab in six patients; and step 3, efficacy and safety in a further 48 patients. The primary study endpoints were safety and response rate.

Results: No dose-limiting toxicity occurred during Steps 1 and 2. Fifty-eight patients were enrolled in Steps 2 and 3 and received XELOX plus bevacizumab. In the 57 patients assessed for response, the overall response rate was 72% (95% confidence interval, 58.5–83.0). Median progression-free survival was 11.0 months (95% confidence interval, 9.6–12.5) and median overall survival was 27.4 months (95% confidence interval, 22.0–not calculated). Eight patients (14%) underwent surgery with curative intent. The most common grade 3/4 adverse events were neurosensory toxicity (17%) and neutropenia (16%).

Conclusions: XELOX plus bevacizumab is effective and has a manageable tolerability profile when given to Japanese patients with metastatic colorectal cancer.

Key words: xelox – bevacizumab – colorectal cancer – Japanese

INTRODUCTION

Colorectal cancer is the third leading cause of cancer deaths worldwide. The number of patients affected by this disease continues to increase steadily (1–3) and ~42 000 deaths occur annually in Japan (3).

FOLFOX4, a bi-weekly schedule of intravenous bolus and infusional 5-fluorouracil/folinic acid plus oxaliplatin (Elplat®) is a widely used regimen for the first-line treatment of metastatic colorectal cancer (MCRC) (4,5). However, oral fluoropyrimidines can replace the intravenous

fluoropyrimidine component of combination regimens. Capecitabine (Xeloda®) is an oral fluoropyrimidine with similar efficacy to bolus 5-fluorouracil/folinic acid when given as first-line treatment for MCRC (6–8) or as adjuvant therapy for stage III colon cancer (9). It has also been successfully combined with oxaliplatin as the capecitabine plus oxaliplatin (XELOX) regimen, which consists of a 21-day intermittent schedule of capecitabine combined with a 3-weekly dose of oxaliplatin (10,11). A pivotal phase III study (NO16966) recently demonstrated that XELOX was non-inferior in terms of efficacy to FOLFOX4 as the first-line treatment for patients with MCRC (12). The same study further showed that adding bevacizumab (Avastin®) to oxaliplatin-based chemotherapy significantly improved progression-free survival (PFS) by 20% in the first-line treatment of MCRC (13). However, most of the clinical development of these regimens has been performed in Europe and the USA, although the NO16966 study included a small number of centers in Central and Eastern Asia (12,13). It has not been clarified if XELOX with the dose and schedule applied mainly to Caucasian patients shows a similar efficacy and toxicity profile in Japanese patients. To address this issue, we conducted a Phase I/II study to evaluate the safety and efficacy of XELOX plus bevacizumab in Japanese patients with MCRC.

PATIENTS AND METHODS

Study Design

A prospective, multicenter, open-label study with a three-step design was conducted to evaluate the efficacy and safety of the commonly used dose of XELOX plus bevacizumab in Japanese patients with MCRC. The purpose of step 1 was to evaluate the initial safety of XELOX in six patients; step 2 was to evaluate the initial safety of XELOX plus bevacizumab in six patients; and step 3 was to evaluate the efficacy and safety of XELOX plus bevacizumab in 48 patients plus the six patients from step 2. The criterion for proceeding to the next phase was the occurrence of dose-limiting toxicity (DLT) in less than or equal to two of six patients. An independent review committee (IRC) was scheduled to evaluate safety immediately after the first cycle in steps 1 and 2. The previous phase I trial determined the recommended dose of the XELOX regimen (14) and DLT was defined as grade 4 neutropenia for 5 days or more, or febrile neutropenia, or grade $\geq$3 neutropenia associated with grade 3/4 complications (e.g. stomatitis, diarrhea); or grade $\geq$3 gastrointestinal toxicities, grade 3 hand-foot syndrome (HFS), grade $\geq$3 peripheral neuropathy, or any grade 4 hematological toxicity or any other clinically significant grade $\geq$3 non-hematological toxicity which did not recover within 2 days with appropriate therapy.

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients participating in this study. The protocol was approved by the independent ethics committee or institutional review board at each site.

Patients

At study enrollment, patients were required to fulfill all of the following criteria: age $\geq$20 and $\leq$74 years, Eastern Cooperative Oncology Group (EGOG) performance status of 0 or 1, life expectancy $\geq$3 months, histologically proven adenocarcinoma of the colon or rectum that was considered to be unrespectable with at least one measurable metastasis (RECIST guidelines) (15), no prior systemic chermotherapy for MCRC, no progression within 6 months of adjuvant therapy completion (if received), neutrophil count $\geq$1500/mm^3, platelet count $\geq$100 000/mm^3, hemoglobin level $\geq$9.0 g/dl, total bilirubin $\leq$1.5 times the institutional upper limit of normal (ULN), aspartate aminotransferase (AST), alanine aminotransferase and alkaline phosphatase $\leq$2.5 times ULN, creatinine $\leq$1.5 times ULN and creatinine clearance $\geq$50 ml/min. Some of the exclusion criteria were as follows: brain tumors or brain metastases, clinically detectable ascites; major surgery, open biopsy or significant traumatic injury within 4 weeks before enrollment, fine needle aspiration biopsy or central venous line placement within 1 week before enrollment, bleeding diathesis or coagulopathy, international normalized ratio $\geq$1.5 within 1 week before enrollment, non-healing bone fracture, urinary protein $\geq$1+ within 1 week before enrollment, uncontrolled hypertension or peptic ulcer, clinically significant cardiovascular disease, chronic, daily treatment with high-dose aspirin ($\geq$325 mg/day) or non-steroidal anti-inflammatory medications, or peripheral neuropathy of at least grade 1. The inclusion and exclusion criteria were almost identical to those used in the NO16966 study (12,13).

Treatment

Oxaliplatin was supplied by Yakult Honsha Co., Ltd (Tokyo, Japan) and capecitabine and bevacizumab were supplied by Chugai Pharmaceutical Co., Ltd (Tokyo, Japan). XELOX consisted of a 2-h intravenous infusion of oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine 1000 mg/m^2 twice daily for 2 weeks of a 3-week cycle. The first dose of capecitabine was given in the evening of day 1 and the last dose in the morning of day 15. Bevacizumab at a dose of 7.5 mg/kg was administered as a 30- to 90-min intravenous infusion before oxaliplatin on day 1 of the 3-week cycle. Treatment was continued until disease progression, intolerable adverse events or withdrawal of consent.

Treatment was to be interrupted if grade 2–4 toxicities occurred. No dose modification of bevacizumab was performed. The dose of capecitabine was to be adjusted for grade 3 or 4 thrombocytopenia or neutropenia, febrile neutropenia or non-hematological toxicities of grade 2 or higher, according to a standard scheme described in detail by Blum et al. (16). The dose of oxaliplatin was to be

reduced to 100 or 85 mg/m^2 if patients experienced grade 3 or 4 thrombocytopenia or neutropenia, febrile neutropenia, or grade 3 non-hematological toxicity, and for grade 3 neurosensory toxicity lasting more than 7 days, or grade 2 neurosensory toxicity persisting between cycles. For grade 3 neurosensory toxicity persisting between cycles, oxaliplatin was to be discontinued. This treatment plan was almost identical to that of the NO16966 study (12,13).

If oxaliplatin and/or bevacizumab were discontinued, treatment with the remaining components could be continued, such as capecitabine with or without bevacizumab after discontinuation of oxaliplatin, and XELOX or capecitabine after discontinuation of bevacizumab. Continuation of oxaliplatin or bevacizumab without capecitabine was not permitted.

Efficacy and Safety Evaluation

Tumor assessments with computed tomography scan were performed within 2 weeks before registration to this study and repeated every 6 weeks. Response rate was evaluated by the investigators according to RECIST version 1.0 (15). Tumor responses were confirmed by the IRC.

PFS was defined as the duration from the date of the first dose of the study drug to the date of first confirmation of disease progression as determined by the IRC, or death from any cause, and censored at the last tumor assessment if a patient withdrew before progression. Overall survival (OS) was defined as the duration from the first dose of study drug to death. Time to response was defined as the time interval from the first dose of study drug to the first detection of $\geq$30% decrease of tumor size assessed by the IRC for patients with a confirmed overall response of PR or CR. Response duration was defined as the time interval from the first detection of $\geq$30% decrease of tumor size to disease progression assessed by the IRC and censored at the last tumor assessment if a patient withdrew before progression.

Safety was assessed weekly for the first eight cycles of the treatment. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (17). All adverse events were evaluated until 28 days after the last dose of study drug.

Statistical Analysis

The primary study endpoints were safety and overall response rate (ORR) as assessed by the IRC. Secondary endpoints were PFS, OS, time to response and response duration.

Forty-eight patients were required to test the null hypothesis (P = p0 or lower) versus the alternative hypothesis (P = pA or higher) with a one-sided α-level of 2.5% and a power of 80% when the critical ORR (p0) was 35% and the expected ORR (pA) was 55%. The total number of patients recruited to receive XELOX plus bevacizumab was estimated to be 54 (6 for Step 2 and 48 for Step 3) to allow for patients who might be ineligible for efficacy evaluation.

ORRs were presented with 95% confidence interval (CI). The probabilities of time-to-event parameters were estimated using the Kaplan–Meier method with 95% CI.

RESULTS

Patient Characteristics

A total of 64 patients were enrolled between February 2006 and November 2006 from 11 centers in Japan. Six patients were enrolled in step 1 and received XELOX and 58 patients were enrolled in steps 2 and 3 and received XELOX plus bevacizumab. All patients (n = 64) were included in the safety analysis. One patient was excluded from the efficacy analysis because he received bevacizumab as part of a different clinical trial. Therefore, six patients were included in the efficacy evaluation of XELOX and 57 patients were included in the efficacy evaluation of XELOX plus bevacizumab.

The baseline demographic characteristics of the enrolled study patient population are shown in Table 1. The median age of the patients treated with XELOX was 58.5 years (range, 40–68 years) and with XELOX plus bevacizumab was 57.0 years (range, 33–74 years). ECOG performance status with XELOX was 0 in all 6 patients, and with XELOX plus bevacizumab was 0 in 50 patients and 1 in 8 patients.

Treatment Duration

In the six patients participating in step 1, the median duration of treatment was 6.5 months (range, 0.5–14 months) with a median of 8.5 treatment cycles (range, 1–17 cycles). XELOX combination therapy was administered for a median of 7.0 cycles (range, 1–17 cycles). One patient subsequently went on to receive a further 6 cycles of capecitabine monotherapy for a total of 13 cycles.

In steps 2 and 3, the median duration of treatment was 7.6 months (range, 0.1–34.8 months) with a median of 10.5 treatment cycles (range, 1–47 cycles). XELOX plus bevacizumab combination therapy was administered for a median of 9.0 cycles (range, 1–27 cycles). After discontinuation of oxaliplatin, 17 patients (29%) continued with capecitabine and bevacizumab combination therapy and received a median of 5.0 cycles (range, 1–34 cycles). Four patients (7%) received XELOX therapy for a median of 2.0 cycles (range, 1–5 cycles) during permanent or temporary discontinuation of bevacizumab.

The median relative dose intensity (ratio of dose received to dose planned) was 0.74 (range: 0.41–1.00) for capecitabine, 0.86 (range: 0.55–1.00) for oxaliplatin and 0.91 (range: 0.58–1.01) for bevacizumab.

Efficacy

At the final data cut-off date (30 June 2009), the median duration of follow-up was 32.0 months. Thirty-three patients

Table 1. Baseline demographic characteristics

Characteristic	XELOX ($n = 6$)		XELOX plus bevacizumab ($n = 58$)	
	No. of patients	%	No. of patients	%
Sex				
Male	5	83	40	69
Female	1	17	18	31
Age				
Median	58.5		57.0	
Range	40–68		33–74	
ECOG performance status				
0	6	100	50	86
1	0	0	8	14
Primary tumor site				
Colon	4	67	31	53
Rectum	2	33	27	47
Metastatic site				
Liver	5	83	45	78
Lung	2	33	28	48
Lymph node	0	0	27	47
Other	3	50	5	9
No. of organs involved				
1	2	33	25	43
2	4	67	21	36
3	0	0	10	17
>3	0	0	2	3
Adjuvant therapy				
Yes	1	17	8	14
No	5	83	50	86

ECOG, Eastern Cooperative Oncology Group.

had died of disease progression and two patients were still receiving study medication. Tumor responses (ORR, time to response, response duration and PFS) are based on the median duration of follow-up of 15.2 months.

The analysis of efficacy is shown in Table 2. The ORR (complete plus partial response) with XELOX was 67% (4/6) (95% CI: 22.3–95.7%), and with XELOX plus bevacizumab was 72% (41/57) (95% CI: 58.5–83.0%). The median PFS with XELOX plus bevacizumab was 11.0 months (95% CI: 9.6–12.5 months) (Fig. 1) and the median OS was 27.4 months (95% CI: 22.0 months–not calculated) (Fig. 2).

Eight patients (14%) treated with XELOX plus bevacizumab underwent surgery with curative intent: none experienced a serious adverse event as a result of surgery and four patients (7%) had no residual disease. The sites of resection being curative by surgery were liver ($n = 7$), lymph node ($n = 1$), cholesyst ($n = 2$) and colon primary tumor ($n = 2$).

Table 2. Analysis of efficacy

Endpoint	XELOX ($n = 6$)	XELOX plus bevacizumab ($n = 57$)
Median progression-free survival, months	8.3	11.0
95% confidence interval	5.8–13.8	9.6–12.5
Median overall survival, months	–	27.4
95% confidence interval	–	22.0-NC
Response rate, %	67	72
95% confidence interval	22.3–95.7	58.5–83.0
Complete response	0	2
Partial response	4	39
Stable disease	1	9
Progressive disease	0	1
Not evaluable	1	6
Median time to response, months	2.6	2.7
95% confidence interval	1.2–NC	1.5–2.8
Median response duration, months	6.4	9.7
95% confidence interval	2.8–11.3	6.7–9.9

NC, not calculated.

Safety

No DLT occurred during either step 1 or step 2. All six patients treated with XELOX and 31 (53%) patients treated with XELOX plus bevacizumab discontinued study treatment because of disease progression. Ten (17%) patients withdrew from XELOX plus bevacizumab because of adverse events, which comprised dehydration and anorexia; gastric varices haemorrhage; enteritis infectious; anorexia, herpes zoster and nausea; neutropenia; AST increased and alanine aminotransferase increased; infected epidermal cyst; peripheral sensory neuropathy; epididymitis; HFS (one patient, respectively). No patient died within 28 days after study medication.

All patients ($n = 64$) experienced at least one adverse event during the study, most of which were mild to moderate in severity (Table 3). The most common adverse events with XELOX plus bevacizumab were neurosensory toxicity (93%), anorexia (90%), fatigue (83%) and HFS (78%). The most common grade 3/4 adverse events were neurosensory toxicity (17%) and neutropenia (16%).

For patients receiving XELOX plus bevacizumab, dose reductions were required for capecitabine in 32 patients (55.2%); the major reasons were HFS ($n = 7$), neutropenia ($n = 6$) and diarrhea ($n = 6$). Capecitabine doses were reduced to 75% of starting dose in 18 patients and to 50% in 14 patients. Dose reductions were required for oxaliplatin in 30 patients (51.7%) due to neurosensory toxicity ($n = 15$), neutropenia ($n = 7$) and other toxicities, and in most of

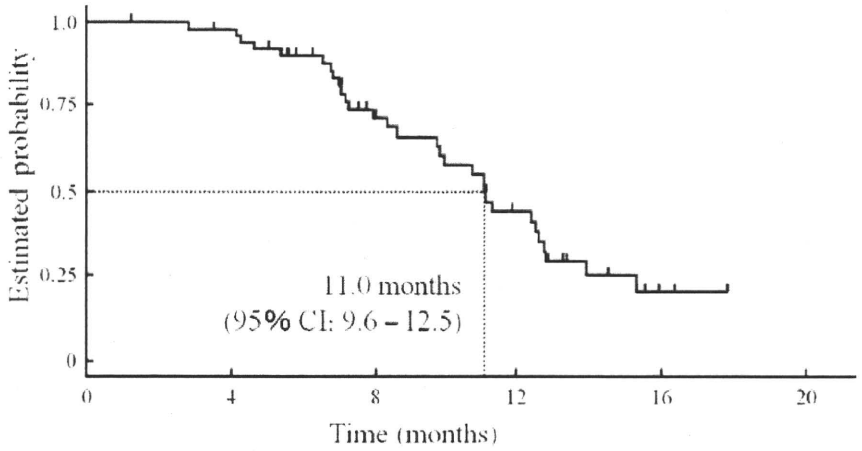

Figure 1. Progression-free survival (XELOX plus bevacizumab).

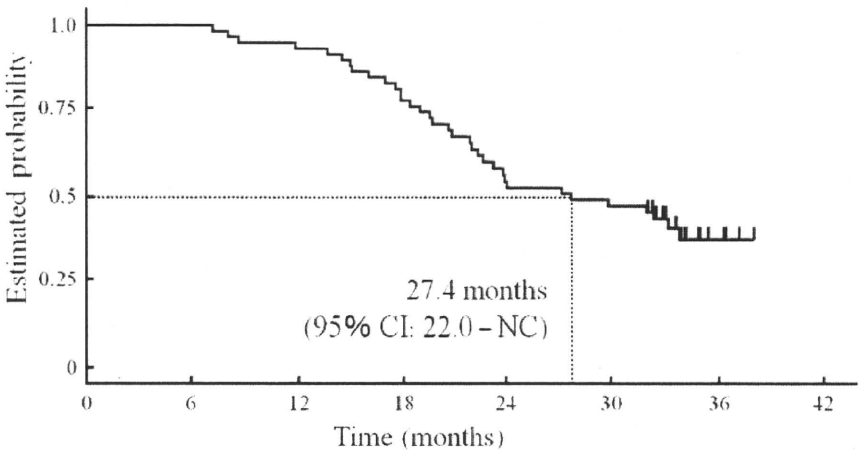

Figure 2. Overall survival (XELOX plus bevacizumab). NC, not calculated.

these patients ($n = 27$) the oxaliplatin dose was reduced to 100 mg/m^2.

DISCUSSION

In this prospective trial for Japanese patients with MCRC, XELOX plus bevacizumab achieved a high response rate of 72%, and eight patients (14%) proceeded to surgery with curative intent. The median PFS and the median OS for XELOX plus bevacizumab were 11.0 and 27.4 months, respectively.

Previous randomized or observational trials which included the XELOX plus bevacizumab regimen as first-line therapy have been conducted mainly in North America and Europe (13,18–22). The NO16966 study showed a longer PFS and OS in the XELOX plus bevacizumab arm compared with the XELOX plus placebo arm in a subgroup analysis, which reported a median PFS of 9.3 versus 7.4 months, HR = 0.77 (95% CI: 0.63–0.94, $P = 0.0026$) and a median OS of 21.6 versus 19.0 months (HR was not shown) (23,24). Furthermore, another phase III trial (CAIRO2) reported a response rate of 50.0%, a median PFS of 10.7 months and a median OS of 20.3 months in the XELOX plus bevacizumab arm (18). The patient baseline demographic characteristics of the enrolled study patient population were similar to those of previous clinical trials in Western patients, except that the proportion of rectal cancer whose prognosis is worse than that of colon cancer was higher in this study (47% versus 23–35%) (4,6–8,11,12). Thus, the efficacy data from our study compares favorably with that reported in other recently conducted studies in predominantly Western patients, although in comparing the efficacy data from 57 patients of this single arm study to those of randomized phase III trials caution should be exercised.

The administration schedule and doses selected for our study were identical to those used in the NO16966 study (12,13). The median relative dose intensity was similar with that in the XELOX plus bevacizumab arm of the NO16966

Table 3. Incidence of common adverse events

Adverse event	XELOX ($n = 6$)				XELOX plus bevacizumab ($n = 58$)			
	Grade 1–4		Grade 3–4		Grade 1–4		Grade 3–4	
	No.	%	No.	%	No.	%	No.	%
Neurosensory toxicity	6	100	1	17	54	93	10	17
Anorexia	5	83	0	0	52	90	2	3
Fatigue	4	67	0	0	48	83	3	5
Hand-foot syndrome	4	67	1	17	45	78	1	2
Nausea	6	100	0	0	43	74	0	0
Pigmentary disturbance	2	33	0	0	36	62	0	0
Stomatitis	2	33	0	0	33	57	1	2
Diarrhea	4	67	0	0	32	55	2	3
Neutropenia	3	50	0	0	30	52	9	16
Vomiting	1	17	0	0	27	47	1	2
Nose bleed	1	17	0	0	23	40	0	0
Proteinuria	0	0	0	0	19	33	3	5
Hypertension	0	0	0	0	19	33	3	5
Thrombocytopenia	2	33	1	17	13	22	4	7
Pulmonary thrombosis	0	0	0	0	1	2	1	2
Jugular vein thrombosis	0	0	0	0	1	2	0	0

study (0.74 versus 0.73 for capecitabine, 0.86 versus 0.81 for oxaliplatin and both 0.91 for bevacizumab). The relative dose intensity was reported in another phase II trial (TREE-2) as well, a median of 0.76 for capecitabine, 0.91 for oxaliplatin and 0.96 for bevacizumab in the XELOX plus bevacizumab arm, whereas the starting dose of capecitabine was reduced to 850 mg/m^2 twice daily and the median duration of the therapy was 19 weeks in that study (14). The safety profile observed in our study was similar to that observed in previous clinical trials with Western patients, including the NO16966 study (12,13,18–22). It is notable that the incidence of grade 3/4 diarrhea was only 3%, which is considerably lower than that reported with XELOX plus bevacizumab in the previous phase II and III studies (19–21%) (12,18,19,22). A lower incidence of diarrhea has been reported in other studies of Japanese or Asian patients treated with fluoropyrimidine-based chemotherapy (25–27). In addition, clinical trials including other oral fluoropyrimidines, such as UFT, have reported lower incidence of grade 3/4 diarrhea in Japanese patients than in Western patients (9.1 versus 22.2%) (28). A reason for this regional variation remains unclear, but it is speculated that differences in dietary folate intake may be a potential explanation (29). Regarding to HFS, although the overall incidence of HFS in our study (78%) was higher than that in the XELOX plus bevacizumab arm of the NO16966 study (39%), the incidence of grade 3 HFS appeared significantly lower (2 versus 12%). The incidence of dose modification (including treatment interruption and delay) due to HFS was similar among the studies (data not shown), as well as the dose intensity of capecitabine as described above. Therefore, the difference in incidences of grade 3 HFS, unfortunately, is not well explained at this time. However, a number of factors may explain this difference. The dose modification of capecitabine due to adverse events other than HFS (e.g. neutropenia, increase of AST, fatigue, anorexia), which occurred at higher incidences in our study compared with the NO16966 study, might be one such factor (data not shown). Difference in frequency of visits could also be factor. Patients received medical examination once every week during first eight cycles in this study, resulting in the treatment interruption in the middle of first 2 weeks of a cycle in four patients among eleven patients who developed grade 2 or grade 3 HFS. Another potential reason might be differences in prophylactic administration (e.g. a moisturizer, steroid ointment, urea ointment etc.). In terms of hematologic toxicities, grade 3/4 neutropenia occurred at 16% in patients receiving XELOX plus bevacizumab in our study which was higher than in the XELOX/XELOX + placebo arm of the NO16966 study (6%) (12), whereas no febrile neutropenia was observed in any patient in our study. The difference in the incidence of grade 3/4 neutropenia may in part be derived from an increased frequency of hematological examination, which was performed once every week in this study in contrast to once every 3 weeks at day 1 in the pivotal phase III study. Known bevacizumab-specific events (i.e. coagulopathy, hypertension, bleeding) were generally mild to moderate in severity in our study, and grade 3/4 events occurred at similar or lower incidence to that reported in Western patients (13). It is concluded that XELOX plus bevacizumab is well tolerated in Japanese patients with MCRC.

Only one patient (2%) treated with XELOX plus bevacizumab experienced grade 3 HFS, compared with an incidence of 13% in a previous phase II study of capecitabine monotherapy (1250 mg/m^2 twice daily) in Japanese patients with MCRC (25). In addition, dose reduction of capecitabine due to HFS was required for less patients in our study (12.1 versus 31.7%). This may be attributable to the 20% reduced dose of capecitabine used in the XELOX regimen compared with capecitabine monotherapy.

In the present trial, six patients received only XELOX. The ORR was 67%, grade 3 adverse events developed in three patients (one event each, respectively) and no significant safety finding was observed. XELOX without bevacizumab is a widely used regimen in a first-line setting for MCRC patients (NCCN guideline) (30). The NO16966 study demonstrated an encouraging efficacy as described above, and another phase III trial showed an ORR of 42%; PFS of 9.3 months; and median OS of 19.9 months in the XELOX arm, with a good safety profile (31). Thus, XELOX seems to be acceptable as an option for a standard regimen for MCRC in Japan, although the data provided in our study is limited to a small population.

In conclusion, in this study, XELOX plus bevacizumab was effective with manageable tolerability profile for Japanese patients with MCRC. The efficacy and safety profile of XELOX plus bevacizumab in this study was consistent with that observed in Western patients, whereas showing a notably lower incidence of diarrhea. Moreover, the XELOX regimen requires only one visit per 3-week cycle for a 2- or 3-h infusion, which may provide a marked advantage over the FOLFOX regimen in terms of the convenience for both patients and clinical staff. Therefore, XELOX plus bevacizumab may be considered as a possible standard treatment for Japanese patients with MCRC.

Acknowledgements

We are indebted to Dr Yuh Sakata, Dr Ichinosuke Hyodo and Dr Kunihisa Miyakawa for their help in the assessment of efficacy and evaluation of safety. We are also grateful to Dr Tetsuo Taguchi, Dr Nagahiro Saijo and Dr Atsushi Ohtsu for supporting the study.

Funding

This work was supported by Chugai Pharmaceutical Co. Ltd and Yakult Honsha Co. Ltd.

Conflict of interest statement

None declared.

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Appendix

The following investigators cared for the patients in this study: Kuniaki Shirao (Oita University, Faculty of Medicine, Yufu, Oita) and Takashi Sekikawa (Toyosu Hospital, Showa University School of Medicine, Tokyo).

Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study)

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Summary

Background Fluorouracil and folinic acid with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) are widely used as first-line or second-line chemotherapy for metastatic colorectal cancer. However, infusional fluorouracil-based regimens, requiring continuous infusion and implantation of an intravenous port system, are inconvenient. We therefore planned an open-label randomised controlled trial to verify the non-inferiority of irinotecan plus oral S-1 (a combination of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate; IRIS) to FOLFIRI as second-line chemotherapy for metastatic colorectal cancer.

Methods Between Jan 30, 2006, and Jan 29, 2008, 426 patients with metastatic colorectal cancer needing second-line chemotherapy from 40 institutions in Japan were randomly assigned by a computer-based minimisation method to receive either FOLFIRI (n=213) or IRIS (n=213). In the FOLFIRI group, patients received folinic acid (200 mg/m²) and irinotecan (150 mg/m²) and then a bolus injection of fluorouracil (400 mg/m²) on day 1 and a continuous infusion of fluorouracil (2400 mg/m²) over 46 h, repeated every 2 weeks. In the IRIS group, patients received irinotecan (125 mg/m²) on days 1 and 15 and S-1 (40–60 mg according to body surface area) twice daily for 2 weeks, repeated every 4 weeks. The primary endpoint was progression-free survival, with a non-inferiority margin of 1·333. Statistical analysis was on the basis of initially randomised participants. This study is registered with ClinicalTrials.gov, number NCT00284258.

Findings All randomised patients were included in the primary analysis. After a median follow-up of 12·9 months (IQR 11·5–18·2), median progression-free survival was 5·1 months in the FOLFIRI group and 5·8 months in the IRIS group (hazard ratio 1·077, 95% CI 0·879–1·319, non-inferiority test p=0·039). The most common grade three or four adverse drug reactions were neutropenia (110 [52·1%] of 211 patients in the FOLFIRI group and 76 [36·2%] of 210 patients in the IRIS group; p=0·0012), leucopenia (33 [15·6%] in the FOLFIRI group and 38 [18·1%] in the IRIS group; p=0·5178), and diarrhoea (ten [4·7%] in the FOLFIRI group and 43 [20·5%] in the IRIS group; p<0·0001). One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment; no treatment-related deaths were reported in the IRIS group.

Interpretation Progression-free survival with IRIS is not inferior to that with FOLFIRI in patients receiving second-line chemotherapy for metastatic colorectal cancer. Treatment with IRIS could be an additional therapeutic option for second-line chemotherapy in metastatic colorectal cancer.

Funding Taiho Pharmaceutical Co Ltd and Daiichi Sankyo Co Ltd.

Introduction

The combination of fluorouracil and folinic acid with either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) has been established as the standard first-line chemotherapy for metastatic colorectal cancer.[1] For second-line chemotherapy for patients resistant to fluorouracil, randomised comparative studies have shown that irinotecan monotherapy was effective.[2,3] Rougier and colleagues[4] showed comparable efficacy of FOLFIRI, FOLFOX, and irinotecan and oxaliplatin (IROX) in patients unresponsive to fluorouracil in a randomised phase 2 study.

Tournigand and colleagues[5] showed that, in patients with metastatic colorectal cancer who were randomly assigned to receive FOLFIRI or FOLFOX as first-line chemotherapy and then crossed over to receive the other as second-line chemotherapy, overall survival was similar in both groups. Consequently, initial treatment with FOLFOX and then second-line treatment with FOLFIRI or vice versa is recommended as standard therapy.[6] However, infusional fluorouracil-based regimens, requiring continuous infusion and implantation of an intravenous port system, are inconvenient and sometimes associated with catheter-related problems such as infection and thrombosis.

Lancet Oncol 2010; 11: 853–60

Published Online August 13, 2010 DOI:10.1016/S1470-2045(10)70181-9

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S-1 is an oral fluoropyrimidine consisting of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in which tegafur is a pro-drug of fluorouracil, CDHP is a dihydropyrimidine dehydrogenase (DPD) inhibitor maintaining the serum concentration of fluorouracil, and potassium oxonate is an inhibitor of orotate phosphoribosyl transferase, reducing gastrointestinal toxicities. Response rates for monotherapy with S-1 are around 35% for colorectal cancer, and it is suggested that DPD inhibition in tumour cells might contribute to antitumour effects because S-1 has been effective against many solid tumours with high DPD expression.[7] Clinically, responses rates of 52·5–62·5% have been reported in phase 2 studies of irinotecan plus S-1 combination therapy, with median progression-free survival of 7·8–8·6 months for first-line treatment for metastatic colorectal cancer.[8–10] These results suggest that the efficacy of IRIS might be comparable to that of FOLFIRI and that IRIS might also be more convenient for both patients and medical facilities.

We did a phase 2/3 randomised study (FIRIS study) to verify the non-inferiority of IRIS to FOLFIRI in patients with metastatic colorectal cancer in whom first-line chemotherapy failed.

Methods

Patients

Inclusion criteria were histologically confirmed colorectal adenocarcinoma; unresectable metastatic disease; age 20–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; withdrawal from first-line chemotherapy due to toxicity or progressive disease, or relapse within 24 weeks after the final dose of preoperative or postoperative chemotherapy; no previous treatment with irinotecan; sufficient oral intake; adequate organ function (white blood cell count 3000–12 000 cells per μL, platelet ≥100 000 per μL, aspartate aminotransferase [AST] ≤100 IU/L, alanine aminotransferase [ALT] ≤100 IU/L, total bilirubin ≤25·7 μmol/L [≤15 mg/L], and creatinine ≤106·1 μmol/L [≤12 mg/L]); and no abnormal electrocardiographic findings within 28 days before enrolment. Exclusion criteria were pregnancy or lactation; second non-colorectal cancer; complications such as ileus, uncontrolled diabetes mellitus, or hypertension; severe diarrhoea; clinically evident gastrointestinal haemorrhage; and ascites or pleural effusion needing treatment.

The protocol of this study was approved by the institutional review board or ethics committee of each institution. The study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients participating in the study.

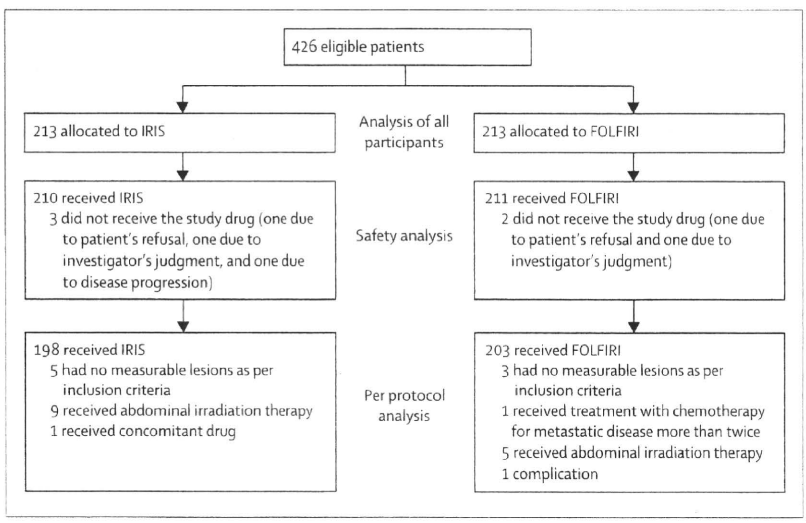

Figure 1: **Trial profile**

Randomisation and masking

Investigators provided the patient's details to the central registration centre through a web-based registration system. After an eligibility check, patients were randomly assigned to receive FOLFIRI or IRIS at the central registration centre by a computer program, by use of a minimisation method with stratification by institution, prior therapy (with or without oxaliplatin), and performance status (0 or 1). Assignment of patients was concealed from the investigator. Treatment assignment was not masked from the investigators or patients.

Procedures

Our randomised, open-label, phase 2/3 study in patients with the second-line metastatic colorectal cancer was done in 40 institutions in Japan (mainly hospitals and medical centres). In the phase 2 portion, safety was assessed in patients treated with either FOLFIRI (30 patients) or IRIS (30). Additionally, the response rate in the first 50 patients in the IRIS group was assessed because IRIS is an unfamiliar regimen in Japan. An independent data and safety monitoring board reviewed our results (safety and efficacy in the phase 2 portion; safety in the phase 3 portion), and approved proceeding to the phase 3 portion. The final analysis was done by use of the combined data from phase 2 and 3 portions.

Patients in the FOLFIRI group received concurrent folinic acid (200 mg/m²) and irinotecan (150 mg/m²) and then a bolus injection of fluorouracil (400 mg/m²) on day 1 and subsequent continuous infusion of fluorouracil (2400 mg/m²) over 46 h, repeated every 2 weeks (4 weeks counted as one cycle). In the FOLFIRI group, the dose of irinotecan was 150 mg/m², the approved dose in Japan.[11] The IRIS group received irinotecan (125 mg/m²) on days 1 and 15 and S-1 (40 mg for patients with body surface area [BSA] <1·25 m²; 50 mg for patients with BSA 1·25<1·5 m²; 60 mg for patients with BSA ≥1·5 m²) twice daily for 2 weeks from days 1–14 and then a 2-week pause, on the basis of results of phase 2 studies.[12,13] We selected this regimen from several documented regimens of irinotecan and S-1 to match the regimen of FOLFIRI in the control arm. Regimens in which irinotecan is given every 2 weeks[12,13] and every 3 weeks are in clinical use in Japan.[8]

In both FOLFIRI and IRIS groups, treatment was delayed until recovery if white blood cell count fell below than 3000 cells per μL, platelets fell below 100 000 per μL, AST or ALT were over 100 IU/L, total bilirubin was higher than 25·7 μmol/L, creatinine was higher than 106·1 μmol/L, the patient experienced diarrhoea of grade one or greater, or other non-haematological toxicities greater than grade two. If a patient experienced a grade four haematological or grade three or higher non-haematological toxicity, the dose was decreased by one level for the next course of treatment, and therapy was resumed.

Treatment was continued until progressive disease, unacceptable toxicity, or patient's refusal to continue treatment. Because molecularly targeted agents such as bevacizumab, cetuximab, and panitumumab were not approved in Japan at the start of our study, no restriction for such agents was specifically placed on treatment before or after the study.

Physical examination, electrocardiography, performance status, and laboratory tests were done at baseline and repeated at least every 2 weeks during treatment. Tumours were assessed at baseline (within 1 month before enrolment), and at 2, 3, and 4 months after enrolment, and thereafter every 2 months until progression. Progression was defined as progressive disease on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, clinical progression judged by the investigator, or death from any cause without progression.

Progression-free survival was counted from the date of randomisation to the date when the progressive disease was first confirmed by the investigator's assessment. For patients without documented progressive disease, data was censored on the date of the last tumour assessment with non-progression status. Overall survival was calculated from the date of randomisation to the date of death or confirmation of survival.

Toxicity was evaluated on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical analysis

The primary efficacy analysis was done with all randomised patients; we also did a per-protocol analysis in which patients in whom there was a major violation such as inclusion or exclusion criteria or protocol treatments were excluded. Safety was assessed in all patients who received at least one dose of the study drug.

The primary objective of our study was to show non-inferiority of IRIS to FOLFIRI for progression-free survival in the whole randomised population. On the basis of data from previous reports in patients with metastatic colorectal cancer who received second-line chemotherapy, median progression-free survival with both FOLFIRI and IRIS was assumed to be 4 months. The steering committee deemed that response assessment could not be repeated more frequently than once a month, so a difference in progression-free survival shorter than 1 month could not be detected precisely. Thus, progression-free survival with IRIS that was 1 month shorter than with FOLFIRI would be acceptable as a lower margin for inferiority, given the expected hazard ratio [HR] of 1·0. The 95% CI upper limit of the HR, calculated using Cox regression analysis with stratification factors other than institution, was prespecified as less than 1·333, meaning the null hypothesis was that median progression-free survival with IRIS would be 1 month shorter than with FOLFIRI. Because 379 events were needed to show non-inferiority with a two-sided α of 0·05 and a power of 80%, a target sample size of 400 patients was required.

Secondary endpoints were overall survival, response rate, and toxicity. Subgroup analyses were done to establish whether therapeutic efficacy was affected by sex, age, histological type, performance status, and prior chemotherapy with or without oxaliplatin. Progression-free and overall survival were estimated using the Kaplan-Meier method. The 95% CI for median progression-free and overall survival was calculated using the method of Brookmeyer and Crowley.[14] All p values were two-sided. All statistical analyses were done with SAS version 8.2. This study is registered with ClinicalTrials.gov, number NCT00284258.

Role of the funding source

The funding source had no role in the study design, data collection, data analysis, or interpretation. All authors had access to all of the data. The corresponding author had final responsibility for decision to submit for publication.

	FOLFIRI (n=213)	IRIS (n=213)
Sex		
Male	123 (57·7%)	120 (56·3%)
Female	90 (42·3%)	93 (43·7%)
Age (years)	63·0 (32–75)	61·0 (29–75)
ECOG performance status		
0	160 (75·1%)	158 (74·2%)
1	53 (24·9%)	55 (25·8%)
Histological type		
Well differentiated	62 (29·1%)	60 (28·2%)
Moderately differentiated	124 (58·2%)	133 (62·4%)
Poorly differentiated	13 (6·1%)	8 (3·8%)
Other	13 (6·1%)	11 (5·2%)
Undetermined	1 (0·5%)	1 (0·5%)
Previous chemotherapy with oxaliplatin		
Yes	128 (60·1%)	129 (60·6%)
No	85 (39·9%)	84 (39·4%)
Number of metastatic sites		
One	92 (43·2%)	88 (41·3%)
Two or more	120 (56·3%)	124 (58·2%)

Data are number (%) or median (range). FOLFIRI=folinic acid, fluorouracil, and irinotecan. IRIS=irinotecan and S-1. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline patient characteristics**

Results

426 patients from 40 institutions in Japan were enrolled in the study from Jan 30, 2006, to Jan 29, 2008, and randomised either to the FOLFIRI or IRIS group (213 patients in each; figure 1). Of the per-protocol population, 203 patients were in the FOLFIRI group and 198 were in the IRIS group; reasons for exclusion are shown in figure 1. All patients who received study treatment (211 patients in the FOLFIRI group and 210 patients in the IRIS group) were included in the safety evaluation. Baseline characteristics were well balanced between the two groups (table 1).

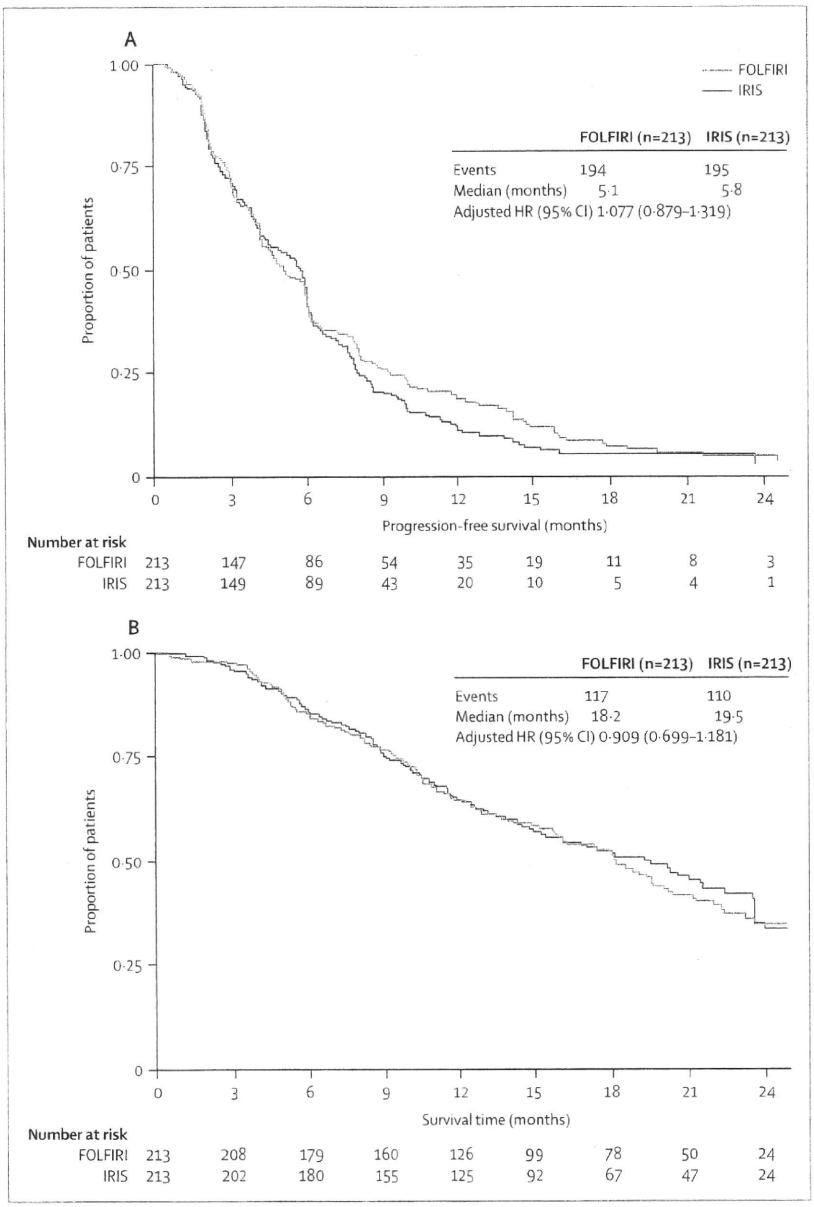

Figure 2: **Progression-free survival (A) and overall survival (B)**
FOLFIRI=infusional fluorouracil, folinic acid, and irinotecan. IRIS=irinotecan plus S-1. HR=hazard ratio.

The mean number of cycles of protocol treatment was 4·7 (range 1–20) for FOLFIRI and 4·9 (1–23) for IRIS. Median relative dose intensities to the planned dose were almost identical: irinotecan 78·3%, bolus fluorouracil 76·9%, and infusional fluorouracil 81·5% in the FOLFIRI group, and irinotecan 78·3% and S-1 88·9% in the IRIS group. Treatments were discontinued because of disease progression in 68·5% (146 patients) in the FOLFIRI group and in 66·2% (141) in the IRIS group, adverse events in 10·8% (23) and in 16·9% (36), and patient's refusal 1·9% (four) and 6·1% (13). 179 patients in the FOLFIRI group and 184 patients in the IRIS group needed a dose delay or dose reduction. Treatment after the trial (ie, treatment after failure of second-line regimen) was given to 159 (74·6%) patients in the FOLFIRI group and 147 (69·0%) in the IRIS group. As third-line treatment, an oxaliplatin-containing regimen was given to 58 (27·2%) patients in the FOLFIRI and 63 (29·6%) in the IRIS group. Molecularly targeted agents as treatments after the trial were used in 24 patients in the FOLFIRI group and 16 in the IRIS group.

As of Dec 31, 2008, collection of progression-free and overall survival data was cut off, with 389 confirmed events (194 FOLFIRI and 195 IRIS). Median follow-up was 12·9 months (IQR 11·5–18·2). Median progression-free survival was 5·1 months in the FOLFIRI group and 5·8 months in the IRIS group. In the entire randomised population, the HR of progression-free survival in the IRIS group compared with the FOLFIRI group was 1·077 (95% CI 0·879–1·319, p=0·039). Similar results were seen in the per protocol population: median progression-free survival was 5·1 months in the FOLFIRI group and 5·7 in the IRIS group (HR 1·050, 95% CI 0·851–1·294).

The data on overall survival are preliminary because of short follow-up. 117 of the 213 patients in the FOLFIRI group and 110 of the 213 patients in the IRIS group died due to any cause. Median overall survival in the entire randomised population was 18·2 months in the FOLFIRI group and 19·5 months in the IRIS group (HR 0·909, 95% CI 0·699–1·181; figure 2). In the per protocol population, median overall survival was 18·1 months in the FOLFIRI group and 19·3 months in IRIS group (HR 0·896, 95% CI 0·685–1·172).

The overall response rate was 16·7% (one patient had a complete response, 28 patients had a partial response) of 174 patients with evaluable response data in the FOLFIRI group and 18·8% (one patient had a complete response, 33 patients had a partial response) of 181 in the IRIS group.

Figure 3 shows the results of subgroup analyses of progression-free survival. Although no interaction was identified between sex, age, histological type, or performance status and therapeutic effects of IRIS compared with FOLFIRI, a statistically significant interaction was noted between prior chemotherapy (with or without oxaliplatin) and therapeutic effects (p=0·030). In the subgroup of patients receiving prior chemotherapy with oxaliplatin, median progression-free survival was

5·7 months in the IRIS group and 3·9 months in the FOLFIRI group (adjusted HR 0·876, 95% CI 0·677–1·133), whereas in patients without prior oxaliplatin treatment it was 6·0 months and 7·8 months, respectively (HR 1·490, 95% CI 1·079–2·059). A similar tendency was noted in the overall survival (figure 4).

Table 2 lists major adverse events. In the two groups, the incidences of adverse events were not markedly different from those previously reported, and none of the adverse events were unexpected. Significantly more patients in the FOLFIRI group experienced grade three or four neutropenia than did those in the IRIS group (110 [52·1%] of 211 patients in the FOLFIRI group *vs* 76 [36·2%] of 210 in the IRIS group; p=0·0012); 33 (15·6%) of patients in the FOLFIRI group and 38 (18·1%) in the IRIS group experienced leucopenia (p=0·5178). The most common non-haematological toxicities were diarrhoea (10 [4·7%] in the FOLFIRI group *vs* 43 [20·5%] in the IRIS group; p<0·0001), anorexia (11 [5·2%] *vs* 23 [11·0%]; p=0·0329), nausea (nine [4·3%] *vs* four [1·9%]; p=0·2593), fatigue (seven [3·3%] *vs* 18 [8·6%]; p=0·0242), and febrile neutropenia (two [0·9%] *vs* 10 [4·8%]; p=0·0205), all at grade three (table 2). One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment; no treatment-related deaths were reported in the IRIS group.

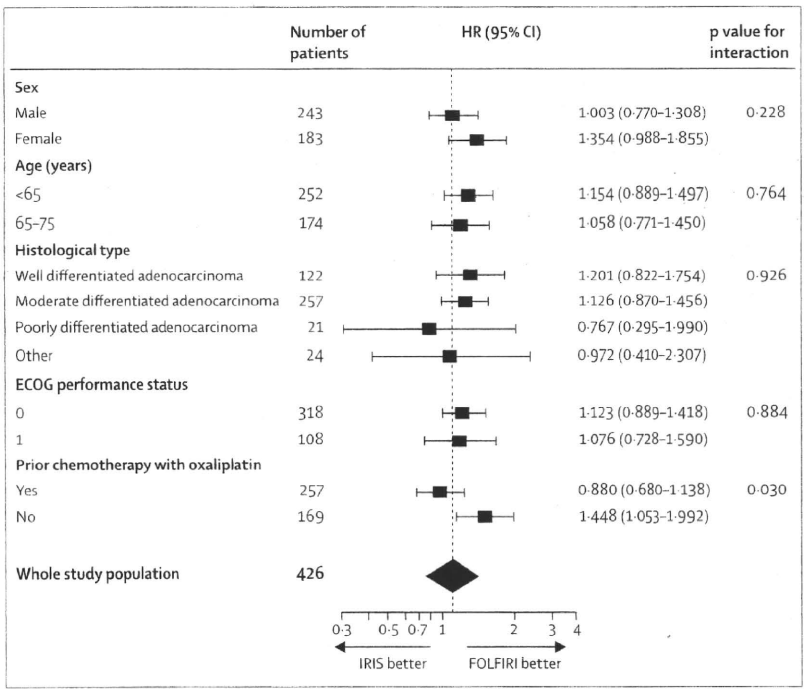

Figure 3: **Subgroup analysis of progression-free survival**
HR=hazard ratio.

Discussion

Our randomised study, comparing FOLFIRI and IRIS as second-line chemotherapy for patients with metastatic colorectal cancer, shows the non-inferiority of IRIS to FOLFIRI. Similar results were obtained in both the entire randomised population and in the more conservative per-protocol analysis. Response rates and overall survival were equivalent between the groups. To our knowledge, this is the first phase 3 trial that shows non-inferiority of oral fluoropyrimidine plus irinotecan therapy to FOLFIRI. From the point of convenience, there has been substantial demand for replacing infusional fluorouracil-based regimens with oral fluorouracil agents. Our study was not designed to collect specific data on working hours of clinicians or the quality of life of patients. However, unlike FOLFIRI, IRIS does not contain infusional fluorouracil and thus does not require a long infusion process, reducing the inconvenience to both patients and clinicians. Additionally, no infuser pump is needed, providing a great advantage to patients. Randomised studies comparing FOLFOX with capecitabine plus oxaliplatin (XELOX) in patients with metastatic colorectal cancer showed that XELOX was non-inferior to FOLFOX.[15,16] By contrast, Fuchs and colleagues[17] reported that progression-free survival with capecitabine plus irinotecan (CapeIRI; 5·8 months) was clearly inferior to that with FOLFIRI (7·6 months) as the first-line chemotherapy for metastatic colorectal cancer, and CapeIRI was associated with a higher incidence of gastrointestinal toxicities and hand-foot syndrome, resulting in discontinuation for reasons other than disease progression.

In our study, the incidence of grade three or worse diarrhoea, fatigue, febrile neutropenia, and anorexia were significantly higher in the IRIS group than the FOLFIRI group. In general, oral fluorouracil-derivative drugs have been shown to be associated with a higher incidence of diarrhoea.[15,17–19] This might also be applicable to S-1. It might be attributable to 2-week treatment with S-1 in IRIS compared with 2-day treatment with fluorouracil in FOLFIRI. However, there was no significant difference in the number of courses or dose intensity between groups. It is thought that all adverse events could be controlled by supportive care, treatment interruptions, or dose reduction, with little effect on treatment continuity. Of note, in the IRIS group, grade four diarrhoea was not detected and fewer of the patients enrolled towards the end of the study experienced grade three diarrhoea.

The incidence of fluorouracil-induced diarrhoea, especially by oral fluoropyrimidines, has been shown to be higher in non-Asian patients than Asian patients.[17,19–21] We speculate that IRIS therapy might also be less feasible in non-Asian patients; therefore, the optimum dose of S-1 in IRIS should be clarified for this population. The reported incidence of hand-foot syndrome due to fluoropyrimidine derivatives containing DPD inhibitors, such as S-1, was low in both Japanese and western trials.[22] In our study, grade three hand-foot syndrome, which is frequently noted with capecitabine-based regimens both in Japanese and non-Asian patients, was not noted in the IRIS group.

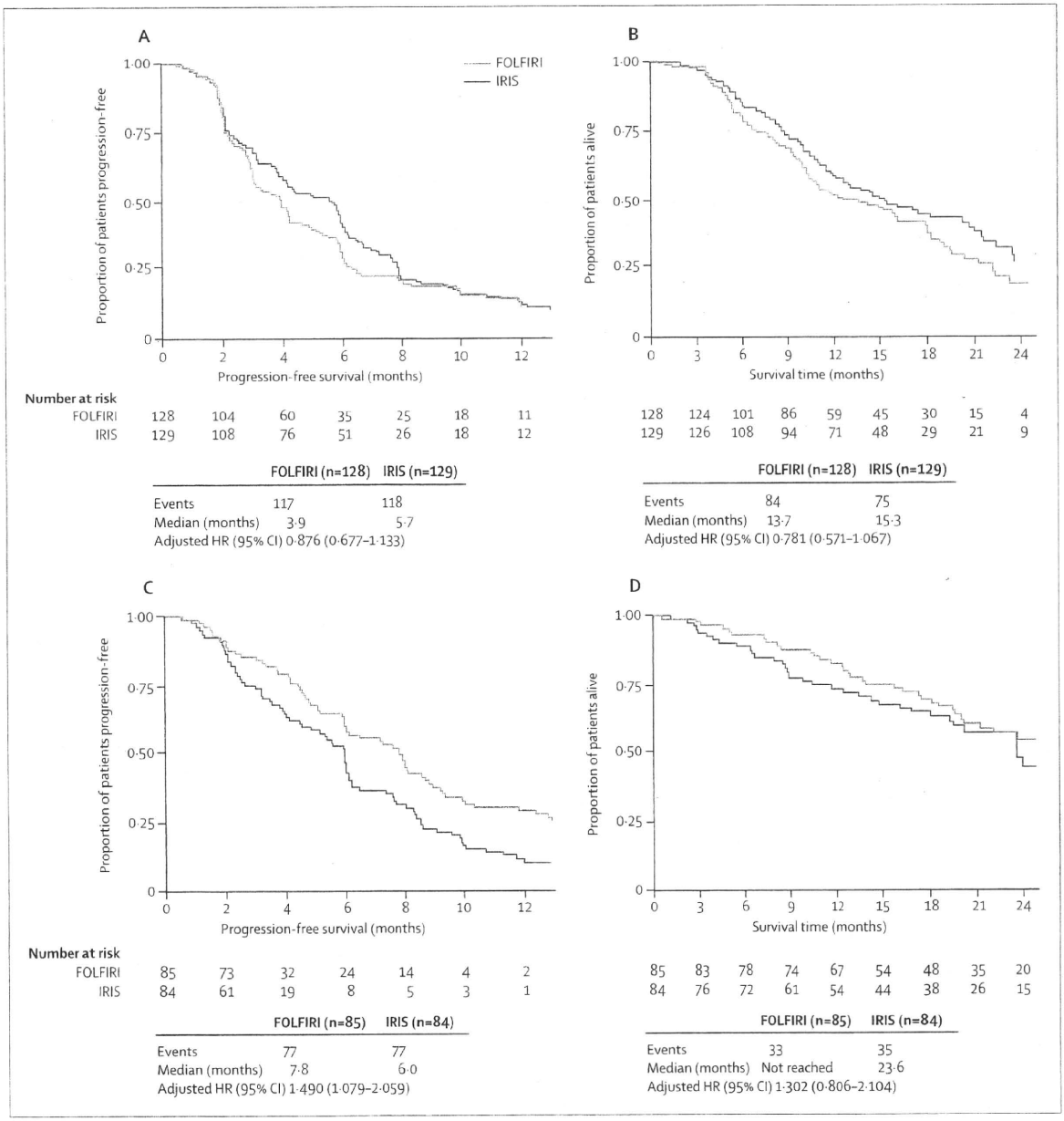

Figure 4: **Survival according to prior chemotherapy**
Progression-free survival with prior oxaliplatin (A). Overall survival with prior oxaliplatin (B). Progression-free survival without prior oxaliplatin (C). Overall survival without prior oxaliplatin (D). FOLFIRI=infusional fluorouracil, folinic acid, and irinotecan. IRIS=irinotecan plus S-1. HR=hazard ratio.

When our trial was started, FOLFOX was already the standard first-line treatment worldwide, but because oxaliplatin had just been launched in Japan, patients who received prior chemotherapy regimens without oxaliplatin were also enrolled. In the subgroup that received prior oxaliplatin, the adjusted HR for progression-free survival of IRIS to FOLFIRI was 0·876 (95% CI 0·677–1·133) suggesting that IRIS was non-inferior to FOLFIRI after failure on oxaliplatin-containing regimens. In this subgroup, the median progression-free survival associated with IRIS was 5·7 months, and much better than the previously reported progression-free survival associated with FOLFIRI in patients who received prior chemotherapy with a fluoropyrimidine and oxaliplatin.[5,23] FOLFOX or FOLFIRI as the first-line chemotherapy and subsequent crossover in the second line is the most common treatment strategy for metastatic colorectal cancer, although there is no evidence of superiority of FOLFIRI over irinotecan alone. In Japan, the approved dose of irinotecan (150 mg/m², every 2 weeks) alone is lower than that in western countries, and monotherapy with irinotecan (350 mg/m², every 3 weeks) could not be used. Both IRIS

	FOLFIRI (n=211)			IRIS (n=210)			p value (grade 3–4)
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	
Neutropenia	179 (84·8%)	76 (36·0%)	34 (16·1%)	139 (66·2%)	54 (25·7%)	22 (10·5%)	0·0012
Leucopenia	170 (80·6%)	32 (15·2%)	1 (0·5%)	154 (73·3%)	32 (15·2%)	6 (2·9%)	0·5178
Anaemia	115 (54·5%)	13 (6·2%)	1 (0·5%)	156 (74·3%)	19 (9·0%)	2 (1·0%)	0·2221
Thrombocytopenia	63 (29·9%)	1 (0·5%)	1 (0·5%)	74 (35·2%)	0 (0·0%)	0 (0·0%)	0·4988
Diarrhoea	125 (59·2%)	10 (4·7%)	0 (0·0%)	167 (79·5%)	43 (20·5%)	0 (0·0%)	<0·0001
Fatigue	144 (68·2%)	7 (3·3%)	0 (0·0%)	153 (72·9%)	18 (8·6%)	0 (0·0%)	0·0242
Febrile neutropenia	3 (1·4%)	2 (0·9%)	0 (0·0%)	10 (4·8%)	10 (4·8%)	0 (0·0%)	0·0205
Mucositis or stomatitis	92 (43·6%)	1 (0·5%)	0 (0·0%)	102 (48·6%)	6 (2·9%)	0 (0·0%)	0·0677
Anorexia	129 (61·1%)	11 (5·2%)	0 (0·0%)	141 (67·1%)	23 (11·0%)	0 (0·0%)	0·0329
Nausea	111 (52·6%)	9 (4·3%)	0 (0·0%)	99 (47·1%)	4 (1·9%)	0 (0·0%)	0·2593

Data are number (%).

Table 2: **Safety analysis**

and FOLFIRI showed longer median progression-free survival than reported in trials of monotherapy with irinotecan.[3,22] Thus, irinotecan-based regimens, such as FOLFIRI and IRIS, delivered every 2 weeks, should be considered after FOLFOX failure, especially in Japan. By contrast, in the subgroup of patients previously treated without oxaliplatin, progression-free survival was longer in the FOLFIRI group than in the IRIS group (HR 1·490, 95% CI 1·079–2·059). In this subset, prior fluorouracil monotherapy (oral, bolus) had failed in some patients. For these patients, FOLFIRI might have greater efficacy than IRIS. Nonetheless, even in this subgroup, median progression-free survival in the IRIS group was 6·0 months and no worse than that previously reported for second-line chemotherapy in patients refractory to fluorouracil alone.[3,24–26]

In each of the subgroups stratified by use or non-use of oxaliplatin, no differences were identified in other patient characteristics between the two groups. There is no clearly understood reason for the interaction between the presence or absence of oxaliplatin and therapeutic effects in the two groups. We speculate that a different mode of fluorouracil administration in FOLFIRI compared with prior therapy might work more effectively than S-1 for the patients without prior therapy with oxaliplatin, and that S-1 might have some salvage effects in patients who received FOLFOX involving bolus and infusional fluorouracil.

Our data have some limitations. First, progression-free survival, the primary endpoint, was assessed on the basis of disease progression established by the investigator at each medical institution. Therefore, caution should be used when our results are compared with those of other studies in which progression-free survival was centrally assessed. Second, around 40% of the patients in this trial were not previously treated with oxaliplatin, since FOLFOX therapy was approved in Japan only just before the study was started. Because FOLFOX is now widely used as first-line chemotherapy in Japan, patients should be carefully selected when our overall results are used to apply IRIS therapy in the clinical setting. However, we believe that the findings from subgroup analyses suggest that IRIS was better than FOLFIRI in patients who received an oxaliplatin-containing regimen as first-line chemotherapy.

In conclusion, progression-free survival with IRIS is not inferior to that with FOLFIRI in patients receiving second-line chemotherapy for metastatic colorectal cancer. IRIS therapy can be an additional treatment option for second-line chemotherapy in metastatic colorectal cancer.

Research in context

Systematic review

Before the study was initiated, we searched the PubMed database for relevant articles using search terms such as "metastatic colorectal cancer", "chemotherapy", "second line", and "phase 3". Based on the relevant articles obtained, the institutional review board reviewed the appropriateness as well as ethical and scientific aspects of the study, on which to base the approval of the study.

Interpretation

Our study demonstrates the non-inferiority of IRIS to FOLFIRI, one of international standard therapies for second-line chemotherapy of metastatic colorectal cancer; thus, IRIS is an option for second-line chemotherapy.

Contributors

IH, SM, NB, YS, HT, YK, MW, and KS, as a steering committee, participated in all phases of this study, including design and writing of the ancillary protocol, analysis, interpretation, and preparation of the report. All authors, with the exception of IH and SM, participated in data collection. SM undertook all analyses. All authors reviewed and helped revise the paper, and approved the submitted version. A list of participating institutions can be found in the webappendix.

See Online for webappendix

Conflicts of interest

KM has received payment for writing the report from Daiichi Sankyo and honoraria from Taiho and Yakult Honsha. NB has received a grant from Taiho; NB's institution has received grants from Taiho. YS has received honoraria from Taiho and Yakult Honsha; YS's institution has received board membership fees and grants from Daiichi Sankyo. AT has received honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha;

AT's institution has received grants from Taiho, Daiichi Sankyo, and Yakult Honsha. SS has received honoraria from Yakult Honsha and lecture fees from Taiho; SS's institution has received grants from Taiho. HB has received board membership fees from Taiho and Daiichi Sankyo, and lecture fees from Taiho, Daiichi Sankyo, Yakult Honsha, and Wyeth; HB's institution has received grants from Taiho, Daiichi Sankyo, Yakult Honsha, Kyowa Hakko Kirin, and Wyeth. TS has received consulting fees from Taiho, honoraria and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Kyowa Hakko Kirin and Wyeth; TS's institution has received grants form Taiho. TD has received honoraria from Taiho, Wyeth, and Yakult Honsha, and lecture fees from Taiho, Daiichi Sankyo, Wyeth, and Yakult Honsha; TD's institution has received grants from Taiho and Yakult Honsha. KI's institution has received grants from Taiho. TN has received honoraria from Taiho, Wyeth, and Yakult Honsha; TN's institution has received grants from Daiichi Sankyo. KY has received lecture fees from Taiho, Daiichi Sankyo, Wyeth, and Yakult Honsha; KY's institution has received grants from Taiho. HT has received board membership fees from Daiichi Sankyo, consulting fees from Yakult Honsha, and honoraria from Taiho and Daiichi Sankyo. TE has received lecture fees from Kyowa Hakko Kirin, Taiho, Wyeth, and Yakult Honsha; TE's institution has received grants from Taiho and Yakult Honsha. ST's institution has received grants from Taiho. HK has received honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha; HK's institution has received grants from Taiho and Daiichi Sankyo, HK's institution has received grants from Daiichi Sankyo. YK has received board membership fees from Daiichi Sankyo, Kyowa Hakko Kirin, Taiho, and Wyeth, and honoraria from Taiho, Daiichi Sankyo, and Yakult Honsha; YK's institution has received grants from Taiho, Daiichi Sankyo, and Yakult Honsha. MW has received board membership fees, honoraria, and lecture fees from Taiho; MW's institution has received grants from Taiho. IH has received board membership fees from Taiho, and consulting fees, honoraria, and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Kyowa Hakko Kirin. SM has received board membership fees from Daiichi Sankyo, consulting fees and honoraria from Taiho and Daiichi Sankyo; SM's institution has received grants from Daiichi Sankyo. KS has received board membership fees from Taiho, honoraria and lecture fees from Taiho, Daiichi Sankyo, and Yakult Honsha, and lecture fees from Wyeth; KS's institution has received grants from Taiho.

Acknowledgments

Our study was supported by an unrestricted grant from Taiho Pharmaceutical Co Ltd, Japan, and Daiichi Sankyo Co Ltd, Japan. We thank all of the patients, their families, and the institutions involved in this study. The authors also thank Yuh Sakata, Yasuo Ohashi, Nobuyuki Yamamoto, Atsushi Ohtsu, Yasuaki Arai, and Junji Tanaka for their contributions to this report.

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2010;40(7)699–701
doi:10.1093/jjco/hyq026
Advance Access Publication 18 March 2010

Clinical Trial Note

Phase II Study of Combination Chemotherapy with Biweekly Cetuximab and Irinotecan for Pre-treated Metastatic Colorectal Cancer Harboring Wild-type *KRAS*

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Received November 29, 2009; accepted February 14, 2010

Standard weekly cetuximab and irinotecan is an effective regimen in heavily pre-treated patients with metastatic colorectal cancer. The aim of this study is to prospectively evaluate the efficacy of combination chemotherapy with biweekly cetuximab and irinotecan in patients with pre-treated metastatic colorectal cancer harboring wild-type *KRAS*. A total of 30 patients will be enrolled at four medical institutions. The primary endpoint is response rate. The secondary endpoints include adverse events, progression-free survival and overall survival. The pharmacokinetics of cetuximab will also be evaluated in five patients.

Key words: colorectal cancer – chemotherapy – cetuximab – irinotecan

INTRODUCTION

Cetuximab, a recombinant, human/mouse chimeric monoclonal IgG1 antibody that specifically targets epidermal growth factor receptor, has been shown to significantly improve the prognosis of metastatic colorectal cancer (MCRC) compared with best-supportive care alone in the third-line setting (1). Furthermore, combining cetuximab with irinotecan results in a higher response rate than cetuximab alone, even in patients with irinotecan-refractory disease (2), suggesting that cetuximab may restore chemosensitivity in these patients. Because of these results, cetuximab plus irinotecan has become the standard chemotherapy in MCRC after failure with 5-fluorouracil, oxaliplatin and irinotecan. Following these two pivotal studies, several retrospective reports suggested that cetuximab is not efficacious in patients with cancers harboring *KRAS* mutations (3–7). Therefore, the indications for cetuximab are considered to be limited to cancers bearing wild-type *KRAS* based on these retrospective studies (8). We conducted a Phase II study employing weekly cetuximab plus biweekly irinotecan for wild-type *KRAS* MCRC (9). An objective response rate of 30.0% and a disease control rate of 80.0% were shown in our previous study (9). Although *KRAS* testing is not yet approved here in Japan as of November 2009, early approval is expected.

On the basis of past pivotal studies, the standard schedule for cetuximab is weekly administration (1,2). In principal, cetuximab is administered weekly with an initial intravenous infusion of 400 mg/m^2 on day 1 infused over 120 min, with subsequent weekly doses of 250 mg/m^2 infused over 60 min. This regimen was used in a Japanese Phase II study (10) and in our prior study (9) with acceptable toxicity. However, in Japan, irinotecan has been commonly administered biweekly. Therefore, if we could achieve similar efficacy and safety with biweekly administration of cetuximab, it would be more convenient both for the patient and for the treating

institution. There are a few reports which evaluated efficacy and feasibility of biweekly administration of cetuximab (11–13). Tabernero et al. conducted a Phase I study of biweekly cetuximab. In their study, cetuximab could be safely administered biweekly at doses between 400 and 700 mg/m^2 (11). They concluded that 500 mg/m^2 was the most convenient and feasible dose. Other two studies using biweekly cetuximab 500 mg/m^2 plus irinotecan showed response rate of 22.5–25% in pre-treated MCRC with the similar toxicity compared with weekly cetuximab (12,13). However, to our best knowledge, no data have been obtained in Japan. Therefore, we have planned a Phase II study of combination chemotherapy with biweekly cetuximab and irinotecan for pre-treated MCRC harboring wild-type *KRAS*. The institutional review board of each participating center approved the study protocol. This study was registered at the UMIN Clinical Trials Registry as UMIN000001951 (http://www.umin.ac.jp/ctr/index.htm).

PROTOCOL DIGEST OF THE STUDY

Purpose

The aim of this study is to evaluate the efficacy and safety of combination chemotherapy with biweekly cetuximab plus irinotecan for the treatment of patients with MCRC that has progressed after irinotecan-, oxaliplatin- and fluoropyrimidine-based chemotherapy.

Study Setting

The study was a multi-institutional prospective Phase II trial, where participating institutions include four specialized centers, as of November 2009.

Endpoints

The primary endpoint is response rate. The tumor response will be assessed objectively after each course according to the Response Evaluation Criteria in Solid Tumors (RECIST), and the maximum response rate will be taken as the antitumor effect for that patient. The secondary endpoints include adverse events defined by Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, progression-free survival and overall survival. A pharmacokinetic (PK) study of cetuximab is also planned to be evaluated in five patients.

Eligibility Criteria

Inclusion Criteria

Prior to enrollment in the study, patients must fulfill all of the following criteria: (i) patients with histopathologically proven metastatic colorectal adenocarcinoma with wild-type *KRAS* are eligible for this study. *KRAS* status is evaluated in each institution using one of the following methods; cycleave PCR (Aichi Cancer Center Hospital) (14,15) or direct sequence methods (BML, Tokyo, Japan). Wild-type *KRAS* means patients without *KRAS* mutations in codons 12 and 13, regardless of the *KRAS* testing method. (ii) Eastern Cooperative Oncology Group performance status 0–2. (iii) The presence of measurable metastatic disease, as defined by the RECIST criteria. (iii) The presence of radiographically confirmed disease progression during previous chemotherapy using irinotecan, or within 3 months after the last chemotherapy dose. (iv) Treatment failure (defined as disease progression/discontinuation due to toxicity) within 6 months of the last dose of fluoropyrimidine- and oxaliplatin-based chemotherapy. (v) Adequate bone marrow reserve (neutrophil count $>1000/mm^3$ and platelet count $>100\,000/mm^3$). (vi) Adequate hepatic function [aspartate aminotransferase and alanine aminotransferase <2.5 times the institutional upper normal limit (<5 times in patients with liver metastases) and total bilirubin <1.5 times the upper normal limit). (vii) Adequate renal function (serum creatinine <2.0 times the upper normal limit).

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) having uncontrollable ascites or pleural effusion; and (ii) having serious co-morbidities such as pulmonary fibrosis or interstitial pneumonia, uncontrollable diabetes mellitus, severe heart disease, other active malignancy, active inflammation or other serious medical conditions.

Treatment Methods

The treatment schedule is based on the results of prior studies (10–12). Cetuximab is administered initially at a dose of 500 mg/m^2 as a 2 h infusion followed by biweekly administration of 500 mg/m^2 as a 1 h infusion. Irinotecan is administered biweekly. The dose of irinotecan (100–150 mg/m^2) is selected by each physician according to each individual patient, based on prior toxicities experienced with irinotecan. Patients receive premedication with antihistamine [e.g. 50 mg diphenhydramine hydrochloride intravenously (i.v.)] to minimize the risk of infusion-related reactions associated with cetuximab. The following anti-emetic treatments are administered on demand: dexamethasone 4 mg prior to cetuximab, and dexamethasone 8–16 mg plus granisetron 1 mg i.v. prior to irinotecan. Grade 3–4 hypersensitivity necessitates cetuximab discontinuation; infusion is slowed to 50% of the prior infusion rate for Grade 1–2 allergic/hypersensitivity reactions. Cetuximab is withheld for Grade 3 skin toxicity until resolution to $\leq$Grade 2. Dose modification and treatment alterations are also performed for irinotecan-associated toxicities. For Grade 4 thrombocytopenia or Grade 3–4 neuropathy, irinotecan is discontinued. The irinotecan dose is reduced by 20 mg/m^2 in the case of Grade 4 neutropenia, Grade 2–3 thrombocytopenia or Grade