Panitumumab in combination with Irinotecan plus S-1 (IRIS) as second-line Therapy for Metastatic Colorectal Cancer

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Abstract

Background Irinotecan plus S-1 (IRIS) is the only oral fluoropyrimidine-based regimen reported to be non-inferior to FOLFIRI and widely used in clinical practice for metastatic colorectal cancer (mCRC) patients. However, the combination of IRIS plus an anti-EGFR agent has not been evaluated previously. This study aimed to investigate the feasibility and efficacy of IRIS with panitumumab as second-line therapy for wild-type *KRAS* mCRC.

Methods Main inclusion criteria were patients with wild-type *KRAS* mCRC refractory to one prior chemotherapy regimen for mCRC, ECOG PS 0-2, and age ≥ 20 years. Patients received panitumumab (6mg/kg) and irinotecan (100mg/m^2) 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 the feasibility of the therapy. The secondary endpoints were response rate (RR), progression-free survival (PFS), and overall survival (OS).

Results A total of 36 patients received protocol treatment in eight centers. Of these, 23 patients (63.9%) completed protocol treatment, demonstrating achievement of the primary endpoint. The most frequent grade 3/4 toxicities were diarrhea (16.7%), acne-like rash (13.9%), and neutropenia (11.1%). The overall RR was 33.3% (12/36). Of these

five underwent conversion surgery. Median PFS and OS were 9.5 months (95% CI 3.5-15.4 months) and 20.1 months (95% CI 16.7-23.2 months), respectively.

Conclusion IRIS plus panitumumab has an acceptable toxicity profile and a promising efficacy in patients with previously treated wild-type *KRAS* mCRC. Accordingly, this regimen can be an additional treatment option for second-line chemotherapy in wild-type *KRAS* mCRC.

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with up to 1 million new cases diagnosed each year [1]. Surgical resection is the only curative therapy for CRC. However, approximately 25% of patients present with metastases at initial diagnosis, and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC [2]. Recently, the outcome of patients with metastatic colorectal cancer (mCRC) has clearly improved with a median survival now reaching nearly 30 months in clinical trials. This improvement is largely due to the development of new chemotherapeutic agents. Combinations of the cytotoxic agents with 5-fluorouracil (5-FU) in 5-FU/leucovorin (LV) /oxaliplatin (FOLFOX) or 5-FU/LV/irinotecan (FOLFIRI) have been established as the standard chemotherapy for mCRC. Moreover, the introduction of monoclonal antibodies against vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) has significantly improved the outcome of patients with mCRC. In these circumstances, approximately 70% of patients who progress after the first line of chemotherapy will receive at least one subsequent line of systemic treatment [3]. This indicates the growing importance of exploring an optimal second-line treatment strategy for mCRC.

Panitumumab is a fully humanized antibody that binds to EGFR and prevents receptor dimerization, tyrosine autophosphorylation of EGFR, and the activation of downstream signaling molecules. Tumor *KRAS* status predicts the efficacy of anti-EGFR agents in mCRC patients and is a well-established biomarker for patient selection [4-6]. Several lines of evidence have shown that panitumumab is active in different lines of treatment and in various combinations with chemotherapy. Peeters and colleagues demonstrated that panitumumab significantly improved the progression-free survival (PFS) in combination with FOLFIRI in second-line treatment of patients with wild-type *KRAS* mCRC [7].

The FOLFOX or FOLFIRI regimens include continuous infusion of fluorouracil, therefore, both of them require implantation of an intravenous port system, which sometimes causes problems such as infection and thrombosis. Muro and colleagues performed a phase II/III randomized study (FIRIS study) to compare irinotecan plus oral fluoropyrimidine, S-1 (a combination of tegafur, 5-chloro-2,4-dihydroxipyridine, and potassium oxonate; IRIS) with FOLFILI as second-line chemotherapy for mCRC, and showed non-inferiority of IRIS to FOLFIRI in terms of efficacy and safety [8]. This enabled the choice of second-line chemotherapy without continuous infusion. However, there has been no previous clinical trial published that investigated safety and efficacy of

IRIS plus an anti-EGFR agent for mCRC. Therefore, in this study, we conducted a prospective, phase II, multicenter trial to investigate the tolerability and efficacy of combination therapy with IRIS plus panitumumab as second-line chemotherapy in patients with wild-type *KRAS* mCRC.

Patients and methods

Study design and eligibility

This study was a multicenter, non-randomized, open-label phase II trial undertaken in eight hospitals (UMIN-CTR registration No. UMIN000004659). The primary endpoint was the feasibility of the therapy. The secondary endpoints were overall response rate (RR), PFS, overall survival (OS), and toxicity. We set feasibility as primary endpoint because it was important to evaluate tolerability and safety profile for subsequent phase 3 study at the time when this study was conducted. The study was performed according to the Declaration of Helsinki and was approved by the independent ethics committees at participating study centers.

Inclusion criteria were: histologically confirmed colorectal adenocarcinoma with

wild-type *KRAS*; unresectable metastatic disease; age ≥ 20 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; presence of at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (ver.1.1) [9] ; withdrawal from first-line chemotherapy due to progressive disease or toxicity, or relapse within 24 weeks after the final dose of preoperative or postoperative chemotherapy; no previous treatment with irinotecan or anti-EGFR agent; sufficient oral intake ability; adequate organ function (hemoglobin ≥ 10 g/dl, leukocytes 3,000-12,000 cells/mm^3, platelets ≥ 100,000/mm^3, serum total bilirubin ≤ 1.5 mg/dl, serum transaminases (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 100 IU/L), serum creatinine ≤ 1.2 mg/dl); and no abnormal electrocardiographic findings within 28 days before enrollment. Exclusion criteria were watery diarrhea; uncontrolled pleural effusion or ascites; active infection; active gastroduodenal ulcer; severe complications such as heart disease or renal disease; mental disorder; history of interstitial pneumonia and pulmonary fibrosis; history of drug hypersensitivity; active concomitant malignancy; and pregnant and lactating females.

Treatment schedule

S-1 was administered orally twice daily for 14 consecutive days, followed by a 14-day rest. The actual dosage of S-1 was decided according to the patient's body surface area [BSA] (40 mg for patients with BSA <1.25 m^2; 50 mg for patients with 1.25 < BSA <1.5 m^2; 60 mg for patients with BSA ≥ 1.5 m^2). Six mg/kg of panitumumab and 100 mg/m^2 of irinotecan were administered as continuous infusions on days 1 and 15. In previous phase2/3 study of the IRIS, irinotecan was administered at a dose of 125 mg/m^2 [8]. However, as adverse drug reactions were intense at that irinotecan dose []125 mg/m^2] in IRIS, recent studies of a combination of IRIS with a biological targeted agent have been conducted at a dose of 100 mg/m^2 [10,11]. Therefore, we chose an irinotecan dose of 100 mg/m^2 in this study. This 28-day cycle was defined as one course of treatment. Initiation of a treatment cycle and administration of irinotecan on day 15 required that neutropenia and thrombocytopenia were grade 2 or lower and non-hematologic toxicities were grade 1 or lower. Administration of panitumumab required confirmation of grade 2 or lower electrolyte abnormalities including hypomagnesemia, hypocalcemia and hypokalemia and grade 2 or lower skin toxicities including pruritus, acneiform dermatitis, skin desquamation, nail disorder, skin fissures, skin laceration, and paronychia. All patients received pre-emptive skin treatment consisting of skin moisturizer applied to face and body daily; topical steroid (0.1% hydrocortisone butyrate applied to face; 0.05%

difluprednate applied to body); and minocycline 100 mg twice per day.

When the patients were judged as resectable after tumor shrinkage by the treatment, they underwent conversion surgery. Protocol chemotherapy was discontinued in the event of disease progression, conversion surgery, unacceptable adverse events, patient's refusal to the treatment, withdrawal of consent, or by physician's decision. A completion of treatment was defined as continuing the protocol treatment until disease progression or until the patient had undergone conversion surgery.

Toxicity and efficacy

Patients who received at least one treatment course were included in toxicity and efficacy analyses. Medical history, physical examination, and safety evaluation were performed prior to treatment and biweekly thereafter. Laboratory tests were also obtained biweekly or more frequently in cases of severe toxicities, and always prior to treatment with irinotecan and panitumumab. Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. CT scanning was performed at 8-week intervals after the start of treatment to assess tumor response in accordance with the RECIST. PFS was defined as the time from registration until

objective tumor progression or death. If the patient underwent conversion surgery, PFS was measured from registration to the date of progression or death after surgery. OS was defined as the time from registration until death from any cause.

Statistical analysis

On the basis of the data from the FIRIS study that more than 23% of the patients who received IRIS discontinued protocol treatment because of adverse events or patient refusal, the expected completion rate was determined to be 75%. In order to confine the 95% confidence interval to +/-15%, the required number of patients was calculated to be 32. Thus, the feasibility was defined as exceeding the lowest rate of the range of completion rate (60%). The target number of patients was set at 35, including 10% of dropouts and excluded patients. PFS and OS were calculated by the Kaplan-Meier method from the date of enrollment.

Results

Patient characteristics

A total of 37 patients were enrolled in this study between January 2011 and November 2013. One patient was not eligible because of his worsening performance status, and 36 patients received more than one planned treatment with IRIS plus panitumumab; they were analyzed for safety and efficacy. Their demographic data are summarized in Table 1. They comprised 24 men and 12 women, with a median age of 65 years (range: 33-84 years). ECOG PS was 0 in 30 patients and 1 in 6 patients. Nineteen patients (52.7%) had liver metastases, 13 (36.1%) lung metastases, 6 (16.7%) lymph node metastases, and 3 (8.3%) peritoneal metastases. Twelve patients were heterozygous for uridine diphosphate-glucuronosyltransferase1A1 (UGT1A1) *6 or UGT1A1*28, one patient was homozygous for UGT1A1*6, and one was heterozygous for both UGT1A1*6 and UGT1A1*28. The median follow-up time was 18.5 months (range, 1.4 – 38.5 months).

Treatment exposure

The median number of treatment cycles was 5 (range, 1 to 18 cycles). Treatment delay and dose reduction occurred in 25 patients (69.4%). Diarrhea was the most frequent

cause of treatment delay, and skin toxicity was a major cause of dose reduction (26.9% and 36.4%, respectively). Treatment was discontinued because of disease progression in 18 patients (50%), conversion to surgery in 5 (13.9%), adverse events in 4 (11.1%), and patient refusal to continue or other reasons in 9 patients (25%). Overall 63.9% (23/36) of patients have completed their protocol treatment, indicating that this study met the primary endpoint. The median relative dose intensities to the planned dose were 88.8% for S-1, 84.8% for irinotecan, and 85.6% for panitumumab, respectively. Adverse events leading to withdrawal in 4 patients were mainly associated with skin toxicity.

Toxicity

All 36 patients were evaluated for toxicity. Table 2 summarizes the treatment-related clinical adverse events. The major grade 3 or 4 adverse events were diarrhea (16.7%), acne-like rash (13.9%), decreased appetite (11.1%), and neutropenia (11.1%). Two patients (5.6%) experienced febrile neutropenia although both of them recovered in a few days by treatment with granulocyte colony-stimulating factor and antibiotics. Most patients (35/36) experienced skin toxicities including paronychia, acne-like rash, and skin laceration. However, the majority of these were grade 2 or lower. Other treatment-

associated symptoms were infrequent or negligible, and there were no treatment related deaths.

Efficacy

Tumor responses are summarized in Table 3. Among the 36 patients, one patient achieved complete response (CR), 11 experienced partial response (PR), 19 had stable disease (SD) and 2 had progressive disease (PD). Three patients were not evaluable for treatment response due to symptomatic deterioration prior to radiological response evaluation. On a per-protocol basis, the response rate (CR + PR) was 33.3%, and the disease control rate (CR + PR + SD) was 86.1%. The median time to response was 63 days [95% confidence interval (CI) 49.6-76.4 days] for patients who responded (CR or PR). Five patients underwent conversion surgery because the physician decided that the metastatic lesion was resectable. Surgical curability types were R0 in one patient, R1 in 2 patients, and R2 in 2 patients. The median PFS was 9.5 months (95% CI 3.5 – 15.4 months) and median OS was 20.1 months (95% CI 16.7 – 23.2 months) (Figure 1A and B).

Discussion

In this phase II study, we demonstrated that our combination therapy with IRIS plus panitumumab was well tolerated and had a promising efficacy against wild-type *KRAS* mCRC as a second-line treatment. To our knowledge, this is the first report to evaluate IRIS plus anti-EGFR antibodies prospectively. The most common reason for treatment discontinuation was disease progression, which occurred in 50 % (18/36) of patients. Five patients (13.9 %) experienced remarkable tumor shrinkage during their protocol treatment and could undergo conversion surgery. Overall 63.9 % (23/36) of patients have completed their protocol treatment, indicating that this study met the primary endpoint. Although this value is relatively low, the previous completion rates of IRIS and FOLFIRI plus panitumumab as second-line therapy for CRCs were 74 and 59 %, respectively, similar to our result (63.9 %). Thus, tolerability and safety profile of IRIS plus panitumumab in this study were similar to those in previous reports on IRIS or FOLFIRI plus panitumumab as second-line therapy in patients with wild-type KRAS mCRC.

The objective response rate was 33.3 %, which was similar to those (23–35 %) in the wild-type *KRAS* population receiving FOLFIRI plus panitumumab in the previous

studies [7, 12]. Besides, 84 % of the disease control rate in this study was relatively higher than those (64–74 %) of FOLFIRI plus panitumumab in the previous studies on FOLFIRI plus panitumumab. In addition, median PFS (9.5 months) and OS (20.1 months) were considerably longer than those of FOLFIRI plus panitumumab (5.9–6.4 and 12.5–14.5 months, respectively) as second-line treatment in previous studies [7, 12].

In our study, the most common grade 3 or 4 hematological adverse event was neutropenia (11.1 %), which was relatively milder than that of the FOLFIRI plus panitumumab regimen in previous reports [7, 12]. On the other hand, the incidence of gastrointestinal adverse events including diarrhea, appetite loss, and stomatitis was relatively high, although severe events (grade 3 or 4) were not frequent. In general, oral fluorouracil agents have been shown to be associated with a higher incidence of gastrointestinal toxicities [13–16]. This might also be applicable to IRIS plus panitumumab. However, it was suggested that all gastrointestinal adverse events of this regimen were controlled by appropriate supportive care or treatment interruptions. Twelve patients (33.3 %) experienced Grade 3 skin-related toxicities including acne-like rash, cutaneous dryness, and paronychia. Our data indicate that the IRIS plus panitumumab regimen increase neither the incidence nor the severity of skin-related toxicities compared to those of FOLFIRI plus panitumumab regimen.

From the point of convenience for the patients, there has been a substantial demand for replacing infusional fluorouracil-based regimens with oral fluorouracil agents. Randomized studies comparing FOLFOX with capecitabine, another oral fluorouracil agent, plus oxaliplatin (CAPOX) in patients with mCRC showed non-inferiority of CAPOX to FOLFOX [13, 17]. In contrast, it has been reported that capecitabine plus irinotecan (CapeIRI) was associated with a higher incidence of gastrointestinal toxicities and hand–foot syndrome and PFS with CapeIRI (5.8 months) was clearly shorter than that with FOLFIRI (7.6 months) as first-line chemotherapy for mCRC [18]. Moreover, capecitabine is not recommended in combination with anti-EGFR antibodies because the efficacy of capecitabine-based regimens could not consistently be confirmed when they were combined with anti-EGFR antibodies, and increased anti-EGFR agent-related side effects, such as skin toxicities, occurred [19]. Thus, IRIS is the only reasonable candidate among oral fluorouracilbased regimens that could be combined with anti-EGFR antibody. Since the IRIS regimen does not include continuous infusion of fluorouracil, IRIS plus panitumumab provides a great advantage to patients over FOLFIRI plus panitumumab. However, tolerance to S-1 is thought to differ in Asian and Caucasian populations. Especially, gastrointestinal toxicities such as diarrhea appear to be more frequent in North American than in Asian [20, 21]. In the current study, all participants were Asian, and this

ethnic uniformity in the patient background is one of the limitations in this study.

In conclusion, the results of this phase II study demonstrated that the combination of IRIS and panitumumab had an acceptable toxicity profile and a promising efficacy in patients with previously treated wild-type KRAS mCRC. This combination can be an additional treatment option for second-line chemotherapy of mCRC.

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Compliance with ethical standards

Conflict of Interest

Tetsuji Takayama has received research funding from Taiho Pharmaceutical Co. Ltd. All other authors declare that they have no conflict of interest relevant to this study.

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Table 1. Baseline demographic and clinical characteristics of patients

Characteristics			No. of patients (n = 36)	%
Gender				
Male			24	66.7
Female			12	33.3
Age (years)				
Median (range)			65 〔33-84〕	
ECOG performance status				
0			30	83.3
1			6	16.7
Primary lesion				
Absent			23	63.9
Present			13	36.1
Metastasis				
Liver			19	52.8
Lung			13	36.1
Lymph nodes			6	16.7
Peritoneal			3	8.3
Bone			1	2.8
Adrenal gland			1	2.8
Prior chemotherapy (cytotoxic agents)				
CAPOX			21	58.3
FOLFOX			13	36.1
5-FU/LV			1	2.8
Other			1	2.8
Prior chemotherapy with bevacizumab				
Yes			31	86.1
No			5	13.9
UGT1A1 polymorphysm				
Wild type			21	58.3
Hetero type	-/*6	-/-	7	19.4
	-/-	-	5	13.9
Double hetero type	-/*6	-	1	2.8
Homo type	*6/*6	-/-	1	2.8
Unknown			1	2.8

ECOG, Eastern Cooperative Oncology Group;
CAPOX, capecitabine/oxaliplatin; FOLFOX, fluorouracil/leucovolin/oxaliplatin;
UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1.

Table 2. Adverse events related to IRIS plus panitumumab occuring in ≥5% of patients treated for metastatic colorectal cancer

Hematological events, n (%)	**Any Grades**	**Grade ≥3**
Leukopenia	10 (27.7)	2 (5.6)
Neutropenia	9 (25.0)	4 (11.1)
Febrile neutropenia	2 (5.6)	2 (5.6)
Anemia	14 (38.8)	1 (2.8)
Thrombocytopenia	8 (22.2)	1 (2.8)
Non-hematological events, n (%)	**Any Grades**	**Grade ≥3**
Diarrhea	22 (61.1)	6 (16.7)
Decreased appetite	22 (61.1)	4 (11.1)
Stomatitis	21 (58.3)	3 (8.3)
Acne-like rash	17 (47.2)	5 (13.9)
Hypomagnesemia	12 (33.3)	2 (5.6)
Fatigue	10 (27.7)	2 (5.6)
Cutaneous dryness	10 (27.7)	2 (5.6)
Hypoalbuminaemia	8 (22.2)	1 (2.8)
Rash	7 (19.4)	3 (8.3)
Paronychia	7 (19.4)	3 (8.3)
Dehydration	7 (19.4)	1 (2.8)
Elevated AST	7 (19.4)	0 (0.0)
Elevated ALT	6 (16.7)	0 (0.0)
Hypocalcemia	5 (13.9)	1 (2.8)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

Table 3. Objective responses of patients with metastatic colorectal cancer receiving IRIS plus panitumumab

	Response						
No. of patients	CR	PR	SD	PD	NE	RR (%)	DCR (%)
36	1	11	19	2	3	33.3	86.1

CR; complete response, PR; partial response, SD; stable disease, PD; progression disease, RR; response rate, DCR; disease control rate

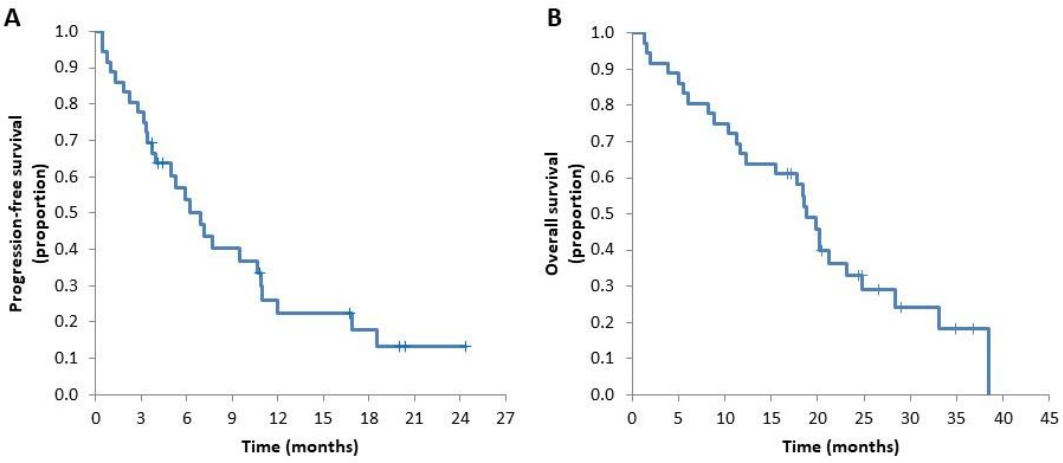

Figure legend

Fig. 1

Kaplan-Meier curve of (A) progression-free survival and (B) overall survival for 36 patients. The median progression-free survival and overall survival were 9.5 months (95% confidence interval, 3.5-15.4 months) and 20.1 months (95% confidence interval, 16.7-23.2 months), respectively.