

Phase II trial of panitumumab with irinotecan as salvage therapy for patients with advanced or recurrent colorectal cancer (TOPIC study)

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Received March 16, 2015; Accepted April 1, 2016

DOI: 10.3892/ol.2016.4532

Abstract. Little is known about the clinical impact of salvage panitumumab with irinotecan for metastatic colorectal cancer (mCRC) patients. The present study conducted a single-arm, multicenter phase II trial for mCRC with skin toxicity prevention program. The subjects were mCRC patients with wild-type *KRAS*, who showed resistance to fluoropyrimidine, oxaliplatin and irinotecan. Panitumumab was administered at a dose of 6 mg/kg every 2 weeks by intravenous infusion over 60 min, and irinotecan was administered at a dose of 100-180 mg/m² every 2 weeks by intravenous infusion over 90 min, depending on the preceding treatment dose. To prevent skin toxicities, a moisturizer was applied and oral antibiotics (100 mg minocycline twice daily) were initiated for 6 weeks. The primary endpoint was the response rate (RR) determined by independent reviewers. Secondary endpoints were the disease control rate (DCR), progression-free survival (PFS) time, overall survival (OS) time and adverse events. A total of 35 patients were enrolled between October 2010 and March 2012. The

median age was 61 years (range, 41-76 years), with 25 male and 10 female patients. The initial irinotecan dose was 150 mg/m² in 19 patients and 180 mg/m² in 1 patient. The remaining patients were treated with ≤120 mg/m². A central review indicated a partial response in 8 patients (22.9%) and stable disease in 6 patients (17.1%), with an RR of 22.9% (95% confidence interval, 12.1-39.0) and a DCR of 40%. The RR of the patients with standard-dose irinotecan (150 or 180 mg/m²) was 30%, although that of low-dose irinotecan (100-120 mg/m²) was 13%. The median PFS time was 2.7 months, and the median OS time was 6.3 months. A grade 3 or above acne-like rash developed in 25.7% of patients. In conclusion, panitumumab and irinotecan as salvage therapy for mCRC *KRAS* wild-type patients with skin toxicity prevention exhibits limited efficacy. In particular, the effect of low-dose irinotecan with panitumumab appears to be clinically insignificant. Routine use of skin toxicity prevention is currently under evaluation.

Introduction

Treatment of metastatic colorectal cancer (mCRC) has progressed considerably over the past decade. In particular, advances in the understanding of the molecular mechanisms involved in carcinogenesis have led to the development of targeted therapy (1). Clinical studies have shown the validity of the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) as therapeutic targets for mCRC patients. Several studies have shown the survival benefits of anti-EGFR therapy for wild-type Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mCRC (2-4). Anti-VEGF therapy has also shown survival benefits in first- and second-line settings (5,6). Recently, several head to head

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Key words: panitumumab, irinotecan, metastatic colorectal cancer

comparisons between anti-EGFR and anti-VEGF therapy were reported for the first-line setting. Although one trial showed higher overall survival (OS) times for anti-EGFR therapy (7), another phase III trial failed to show any survival differences (8). According to these controversial results, anti-EGFR and anti-VEGF therapy are considered of equal importance in the first-line setting. When considering the cosmetic aspects, treatments with anti-EGFR therapy for long period tend to be avoided due to the decrease in skin quality. Due to cumulative skin reactions, anti-EGFR therapy is not preferred in the first-line setting in Japan. However, in cases where a quick response or marked tumor shrinkage is required, anti-EGFR therapy is chosen by oncologists (9). A lack of evidence for the successful use of anti-VEGF as salvage therapy and the impressive results of using bevacizumab beyond progression (BBP) have led to certain oncologists preferring first-line anti-VEGF therapy with the BBP strategy (10,11). However, several detrimental results in anti-EGFR trials have appeared to have resulted in an aversion to using combined therapies as first-line treatment (12,13).

Based on the biological synergistic effect with irinotecan, anti-EGFR tends to be combined even though it is a salvage treatment (14). Two monoclonal antibodies of anti-EGFR have been approved for use in mCRC. The two agents have similar activity, but with certain different results in clinical trials. There is little data on the use of panitumumab with irinotecan in the salvage setting, although cetuximab with irinotecan shows a survival benefit. Recent advances have shown the appeal of a skin toxicity prevention program using panitumumab (15). Panitumumab has several advantageous aspects with regard to schedule and toxicity. Therefore, as further clinical data on salvage panitumumab with irinotecan is required, the present phase II trial for mCRC with a skin toxicity prevention program was conducted to evaluate its clinical efficacy.

Patients and methods

Trial details. The present study is a phase II, single-arm, multicenter study of panitumumab and irinotecan combination therapy. Approval for the study was obtained from the Ethics Committee of Jichi Medical University (Shimotsuke, Japan) and each facility involved, and written informed consent was obtained from all enrolled patients (trial ID, UMIN000004500).

Patients. The inclusion criteria were as follows: Histological diagnosis of unresectable advanced and/or recurrent colorectal cancer; presence of a measurable target lesion; absence of *KRAS* mutation in exon 2 (codons 12 and 13); disease progression or intolerance to irinotecan- and oxaliplatin-based therapy, and had previously received fluoropyrimidines; Eastern Cooperative Oncology Group performance status of 0-2; age ≥ 20 years; neutrophil count $\geq 1,000/\text{mm}^3$; platelet count $\geq 100,000/\text{mm}^3$; total bilirubin level ≤ 1.5 mg/dl; aspartate transaminase (10-35 U) and alanine transaminase levels (5-40 U) ≤ 2.5 times the facility's upper limit of normal (≤ 5 times the respective facility's upper limit in the case of hepatic metastasis); serum creatinine level ≤ 2.0 mg/dl; at least 2 weeks having passed with no treatment since completion of any of the following treatments: and radiotherapy, surgical treatment with organ

resection, chemotherapy, hormone and immunotherapy. The presence or absence of a UDP-glucuronosyltransferase 1-1 measurement was not taken into consideration.

Treatment. Panitumumab (Takeda Pharmaceutical Company, Tokyo, Japan) was administered at a dose of 6 mg/kg every 2 weeks by intravenous infusion over 60 min, and irinotecan was administered at a dose of 100-180 mg/m² every 2 weeks by intravenous infusion over 90 min, depending on the preceding treatment dose. As prophylaxis for anti-emesis, topical steroids and 5-HT₃ receptor antagonists were administered prior to the chemotherapy regimen. This treatment was continued until disease progression, intolerable adverse events and/or upon patient refusal of treatment. If a treatment course could not be initiated due to a neutrophil count $< 1,000/\text{mm}^3$, a platelet count $< 75,000/\text{mm}^3$ and/or other non-hematological toxicity, the treatment was deferred or the dose decreased at the discretion of the attending physician. In the event irinotecan could not be continued due to adverse events, panitumumab monotherapy was continued. To prevent skin toxicities, a moisturizer was applied to the face, arms, legs, neck, back and chest every morning after waking up; sunscreen was applied prior to stepping outside; a topical steroid was applied to the face, arms, legs, neck, back, and chest at bedtime; and oral antibiotics (100 mg minocycline twice daily) were initiated 24 h prior to the first course of treatment. All these treatments were continuously administered for 6 weeks. The decision to continue antibiotics after 6 weeks was left to the discretion of the attending physician.

Evaluation. Patients underwent regular examinations and blood tests as outpatients, and an examination by computed tomography or magnetic resonance imaging was performed every 8 weeks from chemotherapy initiation. The primary endpoint of the present study was the response rate (RR) determined by two independent reviewers. The antitumor effect was determined using the Response Evaluation Criteria in Solid Tumors v. 1.0 (16) by the attending physician, researchers and two independent radiologists. Secondary endpoints included the disease control rate (DCR), the progression-free survival (PFS) time, the OS time and adverse events. PFS time was defined as the period from chemotherapy initiation until progression, and OS time was defined as the period from chemotherapy initiation until mortality. Adverse events were evaluated using the National Cancer Institutes' Common Toxicity Criteria v. 3.0 (Japanese edition) (17). To ascertain each patient's requirement for prophylactic treatment of skin toxicities, patients were asked to keep a diary beginning 24 h prior to the first treatment day until week 6.

Statistical analysis. With the RR threshold set at 10% and the anticipated RR at 25%, 41 patients with measurable responsiveness were required for the α error to be < 0.10 (one-sided) when the true RR was less than the RR threshold and for the statistical power to be $> 90\%$ when the true RR was above the anticipated RR (18,19). Considering that certain patients would be excluded from the analyses, the aim was to enroll 45 patients. PFS and OS were estimated on a survival curve using the Kaplan-Meier method, and the two-sided 95% confidence intervals (CIs) of the standard deviation and median

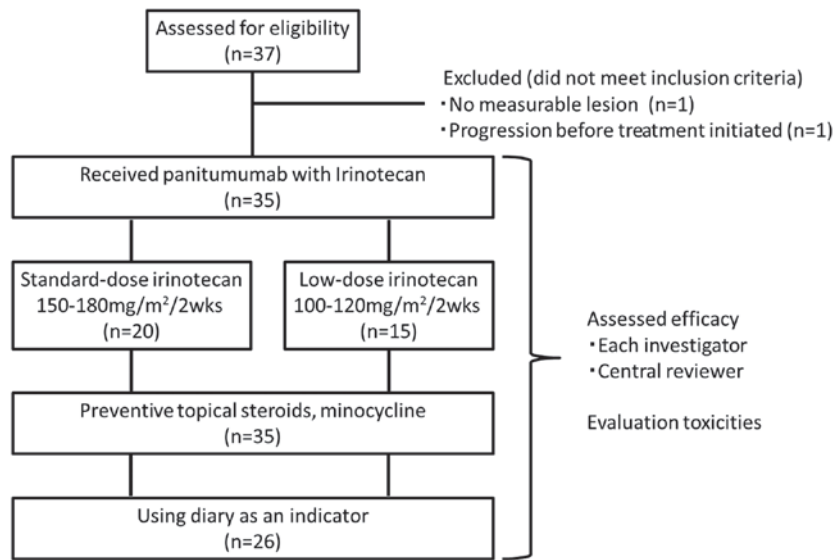


Figure 1. Study schema.

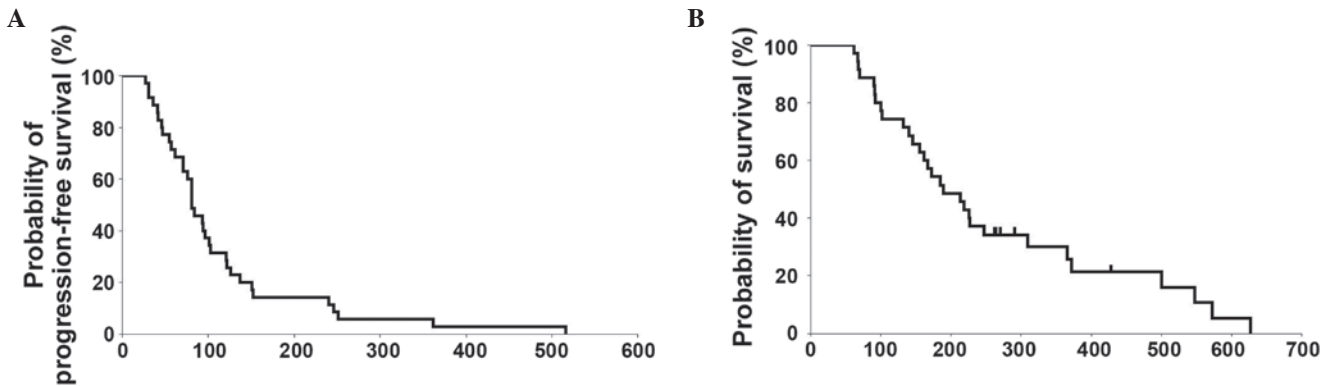


Figure 2. (A) Progression-free survival curves. (B) Overall survival curves.

value were calculated using JMP® software (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. A total of 37 patients from 6 Japanese medical institutions were enrolled between October 2010 and March 2012. The institutions were as follows: Tochigi Cancer Center (Utsunomiya, Japan), Jichi Medical University Hospital (Shimotsuke, Japan), Chiba Cancer Center (Chiba, Japan), Saitama Cancer Center (Saitama, Japan), Ibaraki Central Hospital (Mito, Japan) and Saku Central Hospital (Saku, Japan). Delays in the enrollment process made it difficult for data to be maintained by the study coordinator; as a result, enrollment was terminated. Of the 37 patients enrolled, 1 patient was excluded due to the lack of a target lesion, and 1 patient was excluded due to the inability to receive treatment as a result of disease progression. As a result, the chemotherapy regimen was administered to 35 patients in total (Fig. 1). Patient characteristics are shown in Table I; the median age was 61 years (range, 41-76 years), with 25 male and 10 female patients. The initial irinotecan dose was 150 mg/m² in 19 patients (54%)

and 180 mg/m² in 1 patient. The median number of treatment courses administered was 6 (range, 3-41).

Efficacy. A central review indicated that, of the 35 patients included, 8 patients (22.9%) presented with a partial response and 6 patients (17.1%) with stable disease, with an RR of 22.9% (95% CI, 12.1-39.0) and a DCR of 40% (Table II). An RR of 17.1% (95% CI, 8.1-32.7) and a DCR of 42.9% were recorded. The objective RR of the patients with standard-dose irinotecan (150 or 180 mg/m²) was 30.0% (6/20), although that of low-dose irinotecan (100-120 mg/m²) was 13.3% (2/15). In 2 patients, the chemotherapy was terminated due to surgery being performed. The median PFS time was 81 days (2.7 months; 95% CI, 71-101) and the median OS time was 189 days (6.3 months; 95% CI, 146-247) (Table II). The survival curve is shown in Fig. 2.

Safety. Diaries could be collected from 26 patients, among whom prophylactic treatment for a rash was properly administered in 22 patients (84.6%). Other diaries could not be collected as they had been lost, the patients had refused to complete them or as the patients' symptoms had deteriorated prior to collection. Adverse events are shown in Table III. A grade 3 or above acne-like

Table I. Patient characteristics (n=35).

Characteristic	Value
Gender, n (%)	
Male	25 (71.4)
Female	10 (28.6)
Age, years	
Median	61
Range	41-76
ECOG performance status, n (%)	
0	30 (85.7)
1	5 (14.3)
Primary tumor resected, n (%)	
Yes	26 (74.3)
No	9 (25.7)
Previous adjuvant therapy, n (%)	
Yes	13 (37.1)
No	22 (62.9)
First-line treatment, n (%)	
Oxaliplatin-based therapy	25 (71.4)
Irinotecan-based therapy	5 (14.3)
Others	6 (17.1)
Second-line treatment, n (%)	
Irinotecan-based therapy	28 (80.0)
Oxaliplatin-based therapy	4 (11.4)
Others	3 (8.6)
Prior treatment with bevacizumab, n (%)	
No	4 (11.4)
Yes	31 (88.6)
Last dose of irinotecan of the previous treatment in mg/m ² , n (%)	
180	1 (2.9)
150	19 (54.3)
120	8 (22.9)
100	7 (20.0)

ECOG, Eastern Cooperative Oncology Group.

rash developed in 25.7% of patients, paronychia in 11.4% and dryness in 8.6%. Recovery from the majority of adverse events was possible with the appropriate cessation of the chemotherapy and active interventional therapy. In total, 1 patient succumbed 15 days after the final course of treatment. In this patient, a causal association between mortality and treatment could not be ruled out. In addition, the chemotherapy regimen was discontinued by the attending physician in 4 patients, as these patients refused further treatment due to adverse events.

Discussion

The present study was designed to assess the efficacy of anti-EGFR antibody administered in combination with irinotecan in the salvage setting with skin protection. The objective RR was 23%, the PFS time was 2.7 months and the grade 3

Table II. Efficacy (n=35).

	Central review	Investigator assessment
Overall response rate		
CR, n (%)	0 (0.0)	0 (0.0)
PR, n (%)	8 (22.9)	6 (17.1)
SD, n (%)	6 (17.1)	9 (25.7)
PD, n (%)	21 (60.0)	20 (57.1)
PFS time, days (95% CI)	81 (71-101)	
OS time, days (95% CI)	189 (146-247)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

skin reaction rate was >20%. Relatively low-dose irinotecan cases tended to exhibit a limited response. The study did not reveal any additional efficacy for use of irinotecan and skin toxicity prevention for *KRAS* wild-type patients. Several explanations of these results should be considered with regard to recent oncological topics.

First, the additional effect of salvage irinotecan with panitumumab is controversial. Only small studies have concluded the efficacy of this doublet. GERCOR conducted a single-arm prospective trial showed that, based on biomarker results, the combination of panitumumab and irinotecan was an active third-line regimen in a well-defined population (20). Another Japanese study also suggested promising results with acceptable toxicities (21). Notably, the two studies were non-randomized single-arm study and the sample size was not high. Therefore, the selection bias of these previous studies should be considered.

The next concern is that anti-EGFR had a limited additional efficacy when combined with irinotecan even in several second-line trials. Although panitumumab showed a benefit in overall response and PFS, the change in OS was not significant (22). The PICOLO trial failed to show any additional effect of irinotecan plus panitumumab compared with irinotecan alone (23). Cetuximab also failed to confer any additional effect in the second-line setting (24).

Third, the positive results of cetuximab with irinotecan that have been noted in salvage therapy (14) require further investigation. The study design of this previous study was of a randomized phase II trial and the primary endpoint was RR (14). The sample size of the study was relatively small in order to draw a definitive conclusion. No other controlled data follows irinotecan beyond progression combined with anti-EGFRs. It is therefore time to reconsider the additional effect of irinotecan in the salvage setting.

Finally, several imbalances in anti-EGFR trials should be considered. Previous classical trials have not included the status of the *KRAS* exon 2 mutation. Recent molecular analysis has shown that other minor *KRAS* and *NRAS* mutations, and *BRAF* status are also of importance in the efficacy of anti-EGFR. In the present prospective trial, only *KRAS* exon 2 mutations were tested, and other mutations was not considered.

Table III. Toxicity (n=35).

Symptom	Grade, n				Grade 3/4, %
	1	2	3	4	
Leukopenia	5	6	2	0	5.7
Anemia	23	3	3	0	8.6
Thrombocytopenia	12	1	0	0	0.0
Neutropenia	4	6	1	1	5.7
Febrile neutropenia	0	0	0	0	0.0
Hypomagnesemia	14	5	1	0	2.9
Anorexia	8	7	2	0	5.7
Nausea	5	5	2	0	5.7
Vomiting	4	3	0	0	0.0
Diarrhea	7	4	2	0	5.7
Fatigue	5	9	2	0	5.7
Acneiform rash	11	10	9	0	25.7
Pruritis	4	11	1	0	2.9
Paronychia	8	10	4	0	11.4
Stomatitis	6	9	1	0	2.9
Dry skin	1	4	3	0	8.6
Infusion-related reaction	0	0	0	0	0.0

With regard to skin toxicity prevention, the present study did not reveal a preventive effect with pre-emptive skin treatment. However, in a previous randomized Japanese study, a preventative effect was successfully reported (25). In this randomized study, the importance of skin toxicity prevention was emphasized, although several fundamental problems were evident. The study was a randomized comparison of the conventional and pre-emptive methods in an open-label, non-blinded manner. After previous reports, it would be expected by the investigators and patients that the preventive group would exhibit a higher potential. The lack of a reactive skin program also could be a bias point of this trial. Certain investigators have reported that intensive reactive skin therapy is enough for skin toxicities (26).

Several limitations were noted in the present study. Firstly, the study failed to collect the planned sample. The study was originally designed with >90% statistical power. Only 35 patients were included in the study, the statistical power was decreased to 87%. Furthermore, it was also limited by the fact that the education in skin protection was dependent on the institution. A lack of a full set of biomarker analyses and the low-dose irinotecan administration are reasons for the poor outcome. The present study is therefore not sufficient enough to draw definitive conclusions.

Overall, the present trial was the first negative report of panitumumab and irinotecan in salvage therapy with skin toxicity prevention. The routine use of skin toxicity prevention is not recommended and additional irinotecan also remains under evaluation. In particular, the effect of low-dose irinotecan with panitumumab appears to be clinically insignificant. Further full-set biological analysis is warranted to consider the additional effect of salvage irinotecan combined with anti-EGFR treatment.

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