

A phase II clinical study of combining FOLFIRI and bevacizumab plus erlotinib in 2nd-line chemotherapy for patients with metastatic colorectal cancer

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Abstract

We conducted an open-label single-arm phase II study by combining irinotecan (FOLFIRI) and bevacizumab (BV) plus erlotinib (ER) in 2nd-line chemotherapy for patients with metastatic colorectal cancer (mCRC).

Eligible mCRC patients received 1st-line standard chemotherapy but still had progressive disease. They were given FOLFIRI plus BV at 2.5 mg/kg on day 1 per 2-week cycle, and daily 150 mg ER. The primary endpoint is progression-free survival (PFS).

A total of 122 patients enrolled in the study. Among them, 55.7% were male patients and median age was 58.4 years (29–72 years). Median PFS was 7.1 months (95% CI 4.3–10.2). Median overall survival (OS) was 13.5 months (95% CI 9.7–16.4). No patients had complete responses, 24 patients had partial response (19.6%) and 59 had stable disease (48.4%). The most frequent adverse event (AE) was rash, with 66 patients (54.1%) had grade 3/4 rash. Other frequent grade 3/4 AEs were fatigue (n=36, 29.5%), bleeding (n=31, 25.4%), neutropenia (n=23, 18.9%), and platelets (n=14, 11.5%).

Combining FOLFIRI and BV plus ER in 2nd-line chemotherapy is efficient to treat mCRC patients with acceptable safety.

Abbreviations: AE = adverse event, BV = bevacizumab, ECOG = Eastern Cooperative Oncology Group, ER = erlotinib, FOLFIRI = irinotecan, FOLFOX = oxaliplatin, mCRC = metastatic colorectal cancer, OS = overall survival, PFS = progression-free survival, VEGF = vascular endothelial growth factor.

Keywords: bevacizumab, erlotinib, mCRC, metastatic colorectal cancer, 2nd-line

1. Introduction

Colon and rectal cancer, or colorectal cancer, is one of the most common cancers among both males and females. According to the latest cancer statistics in the United States, colorectal cancer accounts for 8% of the total number of new cancer cases, and 8% to 9% of the total number of cancer deaths in 2014.^[1] Most of the patients with colorectal cancer would develop recurrent or metastatic colorectal cancer (mCRC), and the standard 1st- and 2nd-line treatments include fluorouracil, leucovorin, and irinotecan (FOLFIRI), infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX), or capecitabine plus oxaliplatin.^[2–4]

In 2nd-line chemotherapy for patients with mCRC, combining standard chemotherapy with targeted reagents, such as bevacizumab (BV), a human monoclonal vascular endothelial growth

factor (VEGF) antibody, has shown great promises in improving patients' survivals.^[5–9] In Eastern Cooperative Oncology Group (ECOG) E3200 trial, while comparing the survivals between mCRC patients treated with 2nd-line chemotherapy of FOLFOX4 only, and the patients treated with combining BV and FOLFOX4 (BV+FOLFOX4), the overall survival (OS) and progression-free survival (PFS) were significantly improved from 10.8 months (FOLFOX4) to 12.9 months (BV+FOLFOX4), and 4.7 months (FOLFOX4) to 7.3 months (BV+FOLFOX4), respectively.^[9] These encouraging data then resulted in the direct FDA approval of the usage of BV in 2nd-line chemotherapy for patients with mCRC.^[7]

In addition to antibody against VEGF, recent studies demonstrated that combining VEGF antibody and the antibody against epidermal growth factor receptor, such as erlotinib (ER), could also be beneficial for cancer patients, such as those with melanoma or lung cancer.^[10–12] In a recent phase III Nordic ACT trial, ER was combined with BV in 2nd-line maintenance treatment for mCRC patients previously treated with BV-included 1st-line chemotherapy.^[13] Although the investigators of Nordic ACT trial did not find significant improvement on patients' survival by combining BV with ER, it was a noticeable direction in term of combining VEGF and epidermal growth factor receptor antibodies in the targeted chemotherapy for patients with mCRC.^[13]

In the present study, we conducted a phase II single-arm clinical study to combine BV and ER plus FOLFIRI in 2nd-line chemotherapy for mCRC patients previously received standard 1st-line chemotherapy but still had disease progression. We here report the efficacy and toxicity of this new combinational 2nd-line chemotherapy for mCRC.

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2. Patients and methods

The study protocol was approved by the Ethic Committee of University and informed consent was obtained from the study.

2.1. Patients

This single-arm, open-label phase II study included patients that were older than 18 years but younger than 75 years, had histologically confirmed metastatic colon or rectum cancer with measurable lesion according to Response Evaluation Criteria in Solid Tumors,^[14] had ECOG Performance Score between 0 and 2, had 1st-line xaliplatin-based or FOLFIRI-based chemotherapy but still relapsed, and had not received any treatment involving BV or ER. The patients were excluded if they, metastatic brain tumors, had undergone any major surgeries or immunotherapies within 4 weeks of the enrollment of current study, had uncontrollable hematopoietic conditions or bleeding, had no significant risk of hypertension, or had any significant cardiac, renal, or hepatic malfunctions. The Ethics Committee at the participated institute approved all protocols of current study. And all patients signed consent forms.

2.2. Chemotherapy treatment

For FOLFIRI, patients were put on biweekly cycles with intravenous administration of 1.5-hour 150 mg/m² FOLFIRI and 2-hour 200 mg/m² l-leucovorin, plus 400 mg/m² bolus 5-FU on day 1, followed by 46-hour administration of 1200 mg/m² 5-FU on days 1 and 2. For BV, patients were given 2 intravenous administrations at concentration of 2.5 mg/kg on day 1 for every 2 weeks. For ER, patients were given daily administration of 150 mg until disease progression, intolerable toxic effects, patients' volunteer withdrawal, or death.

2.3. Clinical assessment

PFS was determined to be the primary endpoints with a goal of 6.5 months, based on a null hypothesis of 4.5 months estimated from previous studies.^[9,15] Secondary endpoints were OS, as well as tumor responses, including complete response, partial response, or stable disease, which were examined every 8 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0). The average follow-up period was 9 months. Safety or adverse events (AEs) of patients were examined through clinical or laboratory methods every 4 weeks according to the guideline of National Cancer Institute Common Toxicity Criteria, Common Terminology Criteria for Adverse Events version 3.0.^[16] Dose reduction was not allowed in this study.

2.4. Statistical analysis

PFS and OS were examined by Kaplan–Meier method, unstratified log-rank test and 95% confidence interval (CI). The goal of primary endpoint, PFS, was hypothesized as 6.5 months, opposed to a null assumption of 4.5 months.^[9,15] Originally, we set the power to be 0.9 with 2-side 10% significance. The needed sample size was 186. As on the cut-off date on April, 2014, a total number of 122 patients were included in the study. Therefore, we amended the statistical analysis to have power of 0.8 with 1-side 10% difference. In that case, 110 patients were needed to reject the null assumption.

3. Results

3.1. Patients

Between January 2011 and April 2014, a total number of 122 patients enrolled in the study. The baseline characteristics were listed in Table 1. The median age for the patients was 63.7 years, ranging from 36 to 75 years old. The number of male patients was 71, accounting for 58.2% of total patients. Most patients' ECOG Performance Score was at 0 (n=82, 67.2%). The primary site of carcinoma was colon (n=77, 63.1%). Sixty-seven patients had only 1 site of metastatic tumor (54.9%), and the other 55 patients had 2 or more metastatic sites (45.1%). The majority of the patients had metastatic site at liver (n=73, 58.8%). Three chemotherapy regimens were used during patients' 1st-line treatment setting, FOLFIRI (n=39, 32.0%), oxaliplatin (n=42, 34.4%), and 5-FU (n=41, 33.6%).

3.2. Efficacy

The cut-off date was April 2014. The median follow-up was 9.0 month. Based on a PFS null hypothesis of 4.5 months,^[9,15] we determined to detect a significant improve on PFS of 6.5 months, using 0.8 power and 1-side 10% significance. The results of Kaplan–Meier estimation showed that the median PFS was 7.1 months (95% CI 4.3–10.2) (Fig. 1A). Therefore, the goal of current study was reached. Results also demonstrated that median OS was 13.5 months (95% CI 9.7–16.4) (Fig. 1B).

The response rates were examined according to RECIST (version 1.0) (Table 2). In summary, complete response was not observed among patients. However, 24 patients had partial response (19.6%) and 59 had stable disease (48.4%), resulting in a disease control (DC) rate of 68.0% (n=83). The number of patients had PD was 36 (29.5%).

Table 1
The baseline characteristics of the patients (n=122).

| Characteristics | Patient n, % |
|-------------------------|--------------|
| Median age (range), y | 63.7 (36–75) |
| Sex | |
| Male | 71 (58.2%) |
| Female | 51 (41.8%) |
| ECOG PS | |
| 0 | 82 (67.2%) |
| 1 | 23 (18.9%) |
| 2 | 17 (13.9%) |
| Primary tumor | |
| Colon | 77 (63.1%) |
| Rectum | 38 (36.9%) |
| Both | 7 (5.7%) |
| No of metastatic sites | |
| 1 | 67 (54.9%) |
| ≥2 | 55 (45.1%) |
| Metastatic sites | |
| Liver | 73 (58.8%) |
| Lung | 53 (43.4%) |
| Lymph | 41 (33.6%) |
| Others | 31 (25.4%) |
| First-line chemotherapy | |
| FOLFIRI | 39 (32.0%) |
| XELOX | 42 (34.4%) |
| 5-FU | 41 (33.6%) |

ECOG PS = Eastern Cooperative Oncology Group Performance Status, FOLFIRI = irinotecan, XELOX = oxaliplatin.

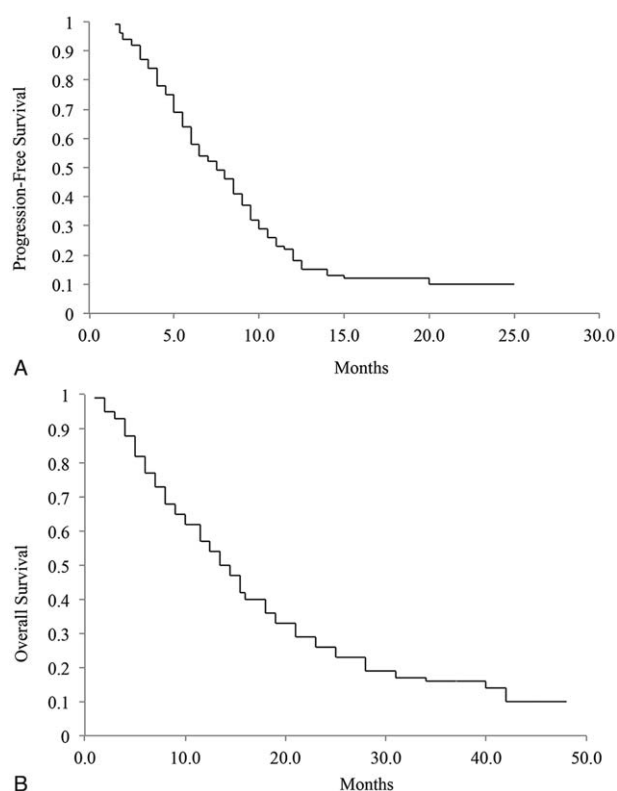


Figure 1. The effect of combining FOLFIRI and bevacizumab plus erlotinib on PFS and OS for patients with metastatic colorectal cancer. Based on a PFS null hypothesis of 4.5 months, we determined to detect a significant improvement on PFS of 6.5 months, using 0.8 power and 1-side 10% significance. The results of Kaplan–Meier estimation showed that the median PFS was 7.1 months (95% CI 4.3–10.2) (A). Results also demonstrated that median OS was 13.5 months (95% CI 9.7–16.4) (B). CI=confidence interval, FOLFIRI=irinotecan, OS=overall survival, PFS=progression-free survival.

3.3. Safety

The AEs were reported in Table 3. Generally, the toxic effects were well tolerated in all 122 patients. Rash was the AE with the highest frequency. It occurred in 92 patients (75.4%). Among them, 66 patients (54.1%) had grade 3 or 4 rash. The high frequency of rash may be attributed to the daily consumption of ER. Other AEs with high frequencies were nausea/vomiting (n=67, 54.9%), bleeding (n=59, 48.4%), fatigue (n=54, 44.3%), and platelets (n=53, 43.4%). Among the grade 3 or 4 AEs, the ones with high frequencies were fatigue (n=36, 29.5%), bleeding (n=31, 25.4%), neutropenia (n=23, 18.9%), and platelets (n=14, 11.5%).

Table 2
The responses of the patients (n = 122).

| Response types | Patient n, % |
|----------------|--------------|
| CR | 0 (0%) |
| PR | 24 (19.6%) |
| SD | 59 (48.4%) |
| PD | 36 (29.5%) |
| Not evaluable | 3 (2.5%) |
| DC | 83 (68.0%) |

CR=complete response, DC=disease control, PD=progressive disease, PR=partial response, SD=stable disease.

Table 3
Adverse events of the patients (n = 122).

| At least 1 adverse event n, % | All adverse events | Grade 3/4 adverse events |
|-------------------------------|--------------------|--------------------------|
| Nausea/vomiting | 67 (54.9%) | 12 (9.8%) |
| Diarrhea | 47 (38.5%) | 11 (9.0%) |
| Fatigue | 54 (44.3%) | 36 (29.5%) |
| Rash | 92 (75.4%) | 66 (54.1%) |
| Asthenia | 41 (33.6%) | 7 (5.7%) |
| Anemia | 16 (13.1%) | 2 (1.6%) |
| Bleeding | 59 (48.4%) | 31 (25.4%) |
| Anorexia | 32 (26.2%) | 4 (3.3%) |
| Constipation | 29 (23.8%) | 11 (9.0%) |
| Thrombocytopenia | 15 (12.3%) | 1 (0.8%) |
| Hypertension | 34 (27.9%) | 7 (5.7%) |
| Heart failure | 27 (22.1%) | 14 (11.5%) |
| Proteinuria | 37 (30.3%) | 9 (7.4%) |
| Peripheral neuropathy | 29 (23.8%) | 8 (6.6%) |
| Neutropenia | 44 (36.1%) | 23 (18.9%) |
| Platelets | 53 (43.4%) | 14 (11.5%) |

4. Discussions

In this open-label, single-arm phase II study, we combined FOLFIRI and BV plus ER in 2nd-line setting to treat mCRC patients who had unsuccessful 1st-line standard chemotherapy. Based on previous studies, we decided the primary endpoint to be PFS with a null assumption of 4.5 months.^[9,15] To achieve a significant improvement, the estimated PFS of current study has to be 6.5 months or longer. As the result of our study from 122 patients with mCRC, we demonstrated that the median PFS was 7.1 months (95% CI 4.3–10.2), suggesting that the new 2nd-line treatment plan of combining FOLFIRI and BV plus ER is effective in improving patients' survival.

Since this is a single-arm study, one would argue that the improved survivals, including PFS and OS, might be solely attributed to adding BV into the chemotherapy, as BV had been shown to improve prognosis of mCRC patients in 2nd-line settings.^[7] This is unlikely the case in our study. In many, if not all the clinical trials combining BV into 2nd-line chemotherapy for patients with mCRC, the standard dosage was either 5 mg/kg on day 1 per 2-week cycle or 7.5 mg/kg on day 1 per 3-week cycle.^[5,6,8,9] In ECOG E3200 trial, the investigator used even higher dosage of BV, 10 mg/kg on day 1 every 2 weeks, to achieve improved OS of 12.9 months, and PFS of 7.3 months.^[9] Unlike previous studies, in the current study, the dosage of BV used was 2.5 mg/kg on day 1 per 2-week cycle, only the half of regularly used dosage in other studies, or even the quarter of the dosage of BV in ECOG 3200 trial. There has been never a report showing clinical benefits on 2nd-line mCRC chemotherapy with such low dosage of BV. Thus, we believe the improved survivals in our study were not due to the single application of BV. Rather, it is contributed by the synergic effects of combining BV and ER. However, to definitively demonstrate the superior efficacy and explore the optimal strategy of this new combinational chemotherapy, a future study with 1 or 2 controlled arms would be needed.

In summary, our data showed that combining FOLFIRI and BV plus ER in 2nd-line chemotherapy is efficient and safe for patients with mCRC.

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