Journal of BUON **16:** 460-463, 2011

ORIGINAL ARTICLE

Safety and efficacy of FOLFIRI-bevacizumab for metastatic colorectal carcinoma as second line treatment

H. Odabas[1], N. Ozdemir[1], M. Isik[1], H. Abali[2], B. Oksuzoglu[1], T. Kos[1], B. Civelek[1], A.N. Babacan[1], U. Dogan[1], N. Zengin[1]

[1]Ankara Numune Education and Research hospital, Division of Internal Medicine, Department of Oncology, Ankara; [2]Baskent University School of Medicine, Department of Medical Oncology, Adana, Turkey

Summary

Purpose: *To evaluate the efficacy and the safety of FOLFIRI-bevacizumab (B) in the 2nd line therapy of metastatic colorectal carcinoma (MCRC).*

Methods: *Between March 2006 and July 2009 35 patients with MCRC were treated with 2nd line therapy FOLFIRI-B (irinotecan 180 mg/m^2 D1, folinic acid 200 mg/m^2 D1, 5-fluorouracil/5 FU 400 mg/m^2 bolus D1, followed by 5 FU 2600 mg/m^2 46-h continuous infusion, and bevacizumab 5 mg/kg D1, every 2 weeks) Their data were collected and analysed.*

Results: *The patient median age was 54 years (range 36-75). One patient (2.8%) had received oxaliplatin-based adjuvant chemotherapy and 33 patients (94.3%) were exposed to oxaliplatin during first line chemotherapy for MCRC. The median follow up period was 12.2 months (range 1.5-37.9). Complete remission (CR) was achieved in 5.7% of the patients and the sum of CR and partial remission (PR) was 11.4%. Disease control (CR+PR+stable disease/SD) was registered in 74.3% of the patients. During follow up, progression (PD) was seen in 32 (91.4%) patients and 23 (65.7%) patients had died. The median progression free survival (PFS) was 7.4 months (95%CI 5.5-9.3) and the median overall survival (OS) 13 months (95%CI 8.8-17.2). Grade 3-4 toxicity requiring delay of chemotherapy was observed in 12 (34.3%) patients with 10 patients (28.6%) having neutropenia and 2 (5.7%) diarrhea.*

Conclusion: *FOLFIRI-B may be an efficient and safe choice in the 2nd line treatment of patients with MCRC previously treated with oxaliplatin.*

Key words: FOLFIRI-bevacizumab, metastatic colorectal carcinoma, second line chemotherapy

Introduction

Nearly 40-50% of all patients with colorectal carcinoma develop metastasis during the course of the disease. Most patients with MCRC may be benefited with a 2nd line treatment after progression [1]. Bevacizumab is a recombinant humanised monoclonal antibody that binds to and neutralises the vascular endothelial growth factor (VEGF), the main mediator of angiogenesis [2]. In phase 2 trials, adding bevacizumab to 5 FU and leucovorin combination (FULV) led to improved clinical outcomes [3]. Recently, a phase 3 randomised multicenter trial showed that adding bevacizumab to FULV and irinotecan combination increased overall response rates and prolonged both the PFS and OS [4]. In recent years, other trials demonstrated that bevacizumab potentiated the efficacy of not only infusional FULV but also irinotecan-containing regimens (FOLFIRI-B) [5-9].

There is no standard 2nd line treatment for patients with MCRC in 2nd line setting after progression on 1st line chemotherapy. The safety and efficacy of irinotecan-containing regimens for MCRC patients progressing after oxaliplatin-containing protocols were previously studied [10-15].

To our knowledge, there are no prospective trials evaluating FOLFIRI-B in the 2nd line treatment of MCRC, but after the results of a phase 3 trial comparing FOLFOX-B (plus bevacizumab) and FOLFOX-4

Correspondence to: Metin Isik, MD. Division of Internal Medicine, Department of Oncology, Ankara Numume Educational and Research hospital, Sihhiye, Ankara 06100, Turkey. Tel: +90 312 3051450, Fax: +90 312 3051348, E-mail: metin1721978@yahoo.com

Received 17-10-2010; Accepted 13-11-2010

(oxaliplatin, infusional 5 FU and leucovorin), the U.S. Food and Drug Administration (FDA) approved bevacizumab for MCRC patients [16,17]. Another pilot study proved the antitumor effect of salvage FOLFIRI-B [18]. Yildiz et al. reported the efficacy and safety of bevacizumab in combination with irinotecan for patients with MCRC [19].

Herein, we aimed to evaluate the efficacy and safety of FOLFIRI-B for MCRC patients given as 2nd line treatment.

Methods

Thirty-five patients with MCRC treated with 2nd line FOLFIRI-B (irinotecan 180 mg/m^2 D1, folinic acid 200 mg/m^2 D1, 5 FU 400 mg/m^2 iv bolus D1, followed by 5 FU 2600 mg/m^2 46-h continuous infusion, and bevacizumab 5 mg/kg, every 2 weeks) between March 2006 and July 2009 were retrospectively analysed. The patient performance status (PS) was evaluated by Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS). Responses were analysed according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria [20]. Side effects were evaluated according to Common Toxicity Criteria for Adverse Events v. 3.0.

Statistical analysis

PFS was defined as the time elapsed from the treatment onset until detection of metastasis or death. OS was defined as the time elapsed from treatment onset till death. Response rates were expressed as percentages. Fischer's exact test and x^2 test were used for nominal variables, Mann-Whitney U test was used for numeric variables. Kaplan-Meier method was used for censored data and log rank test to compare survival rates. All p-values were 2-sided and a value ≤ 0.05 was considered significant. The Statistical Package for Social Sciences, v. 15.0 (SPSS 15.0), software was used for analysis.

Results

Patient characteristics

The characteristics of the patients are shown in Table 1. Twenty-six (74.3%) were male and 9 (25.7%) female, and their median age was 54 years (range 36-75). The most frequent metastatic site was the liver (n=23; 65.7%). After FOLFIRI-B 14 (40%) patients were treated with 3rd line and 9 (25.7%) with 4th or more lines of chemotherapy. The most frequent therapy after FOLFIRI-B was capecitabine (n=8; 22.9%). Other regimens included cetuximab-irinotecan, capecitabine-oxaliplatin (XELOX), FOLFOX, and mitomycin-UFT.

Table 1. Patient characteristics

Characteristics	*N (%)*
Sex	
Male	26 (74.3)
Female	9 (25.7)
Age, years	
Median	54
Range	36-75
ECOG PS	
0-1	27 (77.1)
2-3	8 (22.9)
Primary sites	
Colon	22 (62.9)
Rectum	13 (37.1)
Metastatic sites	
Liver	23 (65.7)
Lung	12 (34.3)
Other	19 (54.3)
No. of metastatic sites	
1	14 (40)
2 and more	21 (60)
First line treatment	
FOLFOX	33 (94.3)
Capecitabine	2 (5.7)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, FOLFOX: folinic acid, fluorouracil, and oxaliplatin

Efficacy

The median follow up period was 12.2 months (range 1.5-37.9). CR was achieved in 2 (5.7%) patients, PR in 2 (5.7%), SD in 22 (62.9%), and PD in 9 (25.7%) patients. Disease control rate was 74.6% (26 patients) (Figure 1). At the time of analysis PD was registered in

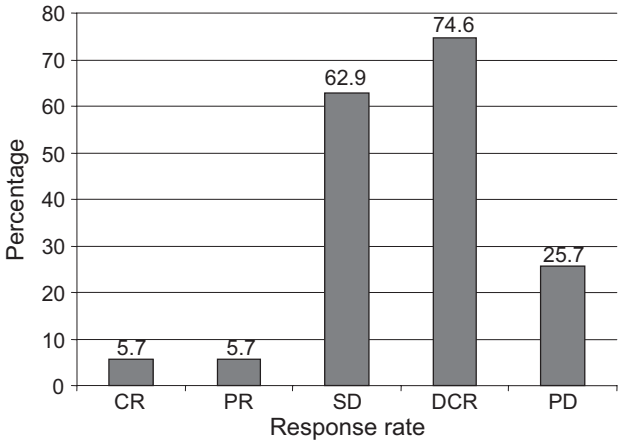

Figure 1. Response rate. CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, DCR: disease control rate

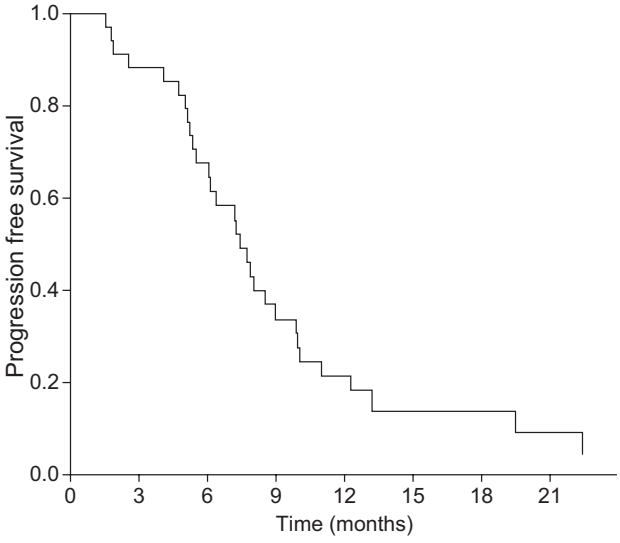

Figure 2. Progression-free survival.

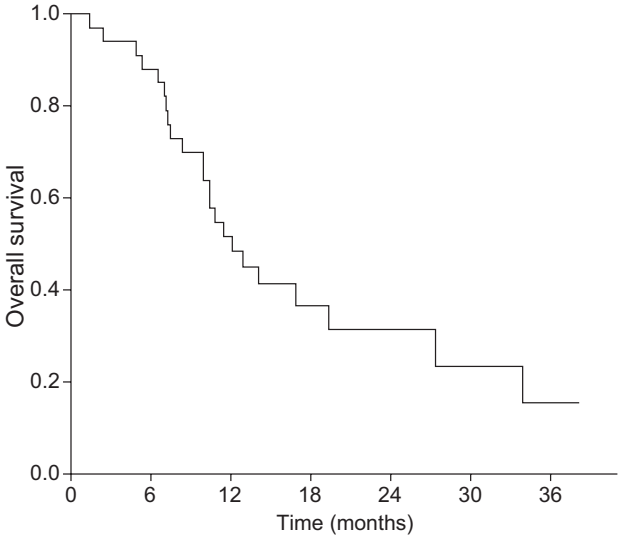

Figure 3. Overall survival.

32 (91.4%) patients and 23 (65.7%) patients had died. Median PFS was 7.4 months (95% CI 5.5-9.3), and median OS 13 months (95% CI 8.8-17.2) (Figures 2 and 3).

Toxicity

The median number of cycles was 8 (range 1-14) and generally FOLFIRI-B was well tolerated. None of the patients died because of toxicity. Three patients (8.6%) abandoned chemotherapy on their own decision. Toxicities are shown in Table 2. Chemotherapy was postponed in 12 (34.3%) patients due to grade 3-4 toxicities: 10 (28.6%) due to neutropenia and 2 (5.7%) due to diarrhea. Dose reduction (25% for 5 FU and irinotecan) was necessary for 5 (13.8%) patients: 3 (8.6%) for grade 3/4 neutropenia, 1 (2.6%) for grade 3/4 diarrhea and 1 (2.6%) for grade 3/4 nausea and vomiting. The most frequent grade 3 and 4 hematologic toxicity was neutropenia (28.5%), neutropenic fever (8.6%), thrombocytopenia (5.7%) and anemia (2.9%). Grade 3 and 4 nausea and vomiting was observed in 8.6% and diarrhea in 5.7% of the patients. Venous thrombosis occurred in 5.7% of the patients.

Table 2. Frequency of common toxicities

Toxicity	*Grade 1-2 N (%)*	*Grade 3-4 N (%)*
Anemia	10 (28.5)	1 (2.9)
Neutropenia	8 (22.8)	10 (28.5)
Thrombocytopenia	4 (11.4)	2 (5.7)
Nausea/Vomiting	5 (14.3)	3 (8.6)
Weakness	3 (8.6)	1 (2.9)
Diarrhea	3 (8.6)	2 (5.7)
Mucositis	5 (15.3)	1 (2.9)

Discussion

We studied the efficacy and safety of FOLFIRI-B for MCRC patients in the 2nd line setting where there is no standard of care. The choice of treatment usually depends on the previous palliative and adjuvant protocols and the patients' PS. Irinotecan-based regimens after oxaliplatin-based ones in MCRC show response rates ranging from 4 to 27%, median PFS 4.1-7.5 months and OS between 9.5 to 14 months [10-15]. In their landmark phase 3 trial, Tournigand et al. found that the response rate of FOLFIRI after FOLFOX6 was 4%, and the PFS was 2.5 months [21], much worse than our figures of 11.4% and 7.0 months, respectively, probably owing to the addition of bevacizumab. In another pilot study of FOLFIRI-B in 14 patients progressing after irinotecan and oxaliplatin-based regimens, the response rate was 28.5%, PFS 3.9 months and OS 10.9 months. In our study FOLFIRI-B was shown to be efficacious, but the OS and PFS were worse compared to FOLFOX-B, which may be explained by its retrospective nature and the small sample size, previous exposure to oxaliplatin and doses of leucovorin and bevacizumab lower than usual [18]. Yildiz et al. studied the efficacy and safety of irinotecan and bevacizumab combination in 40 patients as 2nd line treatment and found response rate of 20%, PFS 6 months and OS 14 months [19]. In our trial, the overall response rate was 11.4%, PFS 7.4 months and OS 13 months with FOLFIRI-B. When compared with FOLFOX-B, the OS and PFS were similar but the response rate was lower. Giantonia et al. in their trial, used a rather higher bevacizumab dose of 10 mg/m^2, in other

words 2-fold higher bevacizumab dose than the dose in our trial [16]. In the trial of Yildiz et al. the dosage of bevacizumab was 5 mg/m^2 but only 22.9% of the patients had bevacizumab in combination with FOLFIRI and for the other patients bevacizumab was combined with infusional 5 FU or irinotecan [19]. Giantonia et al. did not state the number of metastatic sites but in the trial by Yildiz et al. the ratio of patients with 2 or more metastatic sites was 42.5%, while it was 60% in our trial. In those trials, the ratio of patients with ECOG PS 0-1 was 90% [16,19], while it was only 77.1% in our trial.

As for toxicities, FOLFIRI-B is well tolerated and safe [5]. In our trial, grade 1-2 toxicities were low. Neutropenia was the most frequent grade 3-4 side effect. Grade 3-4 diarrhea was observed only in 5.7% of the patients.

Most of the patients with MCRC are treated with FOLFIRI-B in the 1st line treatment, therefore alternative regimens are looked for in the 2nd line. On the other hand, although there is a trial [22] with limited number of patients showing good efficacy of FOLFOX-B in the 2nd line setting, there is no randomised prospective trial in this field.

In conclusion, despite its limitations, our study showed efficacy and good tolerability of FOLFIRI-B as 2nd line treatment of MCRC patients after oxaliplatin-based regimens.

References

1. Rougier P, Lepere C. Second-line treatment of patients with metastatic colorectal cancer. Semin Oncol 2005; 32 (6 Suppl 9): 48-54.
2. Presta LG, Chen H, O'Connor SJ et al. Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 1997; 57: 4593-4599.
3. Kabbinavar F, Hurwitz HI, Fehrenbacher L et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003; 21: 60-65.
4. Hurwitz H, Fehrenbacher, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350: 2335-2342.
5. Fuchs CS, Marshall J, Mitchell E et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. J Clin Oncol 2007; 25: 4779-4786.
6. Grothey A, Sugrue MM, Purdie DM et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE). J Clin Oncol 2008; 26: 5326-5334.
7. Van Cutsem E, Rivera F, Berry S et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol 2009; 20: 1842-1847.
8. Sobrero A, Ackland S, Clarke S et al. Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. Oncology 2009; 77: 113-119.
9. Kopetz S, Hoff PM, Morris JS et al. Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: efficacy and circulating angiogenic biomarkers associated with therapeutic resistance. J Clin Oncol 2010; 28: 453-459.
10. Ulrich-Pur H, Kornek GV, Fiebiger W et al. Multicenter phase II trial of dose-fractionated irinotecan in patients with advanced colorectal cancer failing oxaliplatin-based first-line combination chemotherapy. Ann Oncol 2001; 12: 1269-1272.
11. Stickel F, Jüngert B, Brueckl V et al. Weekly high-dose 5-fluorouracil as 24-h infusion and folinic acid (AIO) plus irinotecan as second- and third-line treatment in patients with colorectal cancer pre-treated with AIO plus oxaliplatin. Anticancer Drugs 2003; 14: 745-749.
12. Recchia F, Saggio G, Nuzzo A et al. Multicentre phase II study of bifractionated CPT-11 with bimonthly leucovorin and 5-fluorouracil in patients with metastatic colorectal cancer pretreated with FOLFOX. Br J Cancer 2004; 91: 1442-1446.
13. Souglakos J, Vardakis N, Androulakis N et al. Irinotecan plus weekly 5-fluorouracil and leucovorin as salvage treatment for patients with metastatic colorectal cancer: A phase II trial. J BUON 2005; 10: 47-52.
14. Mabro M, Artru P, André T et al. A phase II study of FOLFIRI-3 (double infusion of irinotecan combined with LV5FU) after FOLFOX in advanced colorectal cancer patients. Br J Cancer 2006; 94: 1287-1292.
15. Sørbye H, Berglund A, Tveit KM et al. Secondary treatment and predictive factors for second-line chemotherapy after first-line oxaliplatin-based therapy in metastatic colorectal cancer. Acta Oncol 2007: 46: 982-988.
16. Giantonio BJ, Catalano PJ, Meropol NJ et al. Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007; 25: 1539-1544.
17. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer. Oncologist 2007; 12: 356-361.
18. Kwon HC, Oh SY, Lee S, Kim SH, Kim HJ. Bevacizumab plus infusional 5-fluorouracil, leucovorin and irinotecan for advanced colorectal cancer that progressed after oxaliplatin and irinotecan chemotherapy: a pilot study. World J Gastroenterol 2007; 13: 6231-6235.
19. Yildiz R, Buyukberber S, Uner A et al. Bevacizumab plus irinotecan-based therapy in metastatic colorectal cancer patients previously treated with oxaliplatin-based regimens. Cancer Invest 2010; 28: 33-37.
20. Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92: 205-216.
21. Tournigand C, André T, Achille E et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004; 22: 229-237.
22. Koyama M, Murata A, Kimura Y et al. Bevacizumab in combination with mFOLFOX or FOLFIRI for previously treated metastatic colorectal cancer. Gan To Kagaku Ryoho 2010; 37: 1069-1073.