Original Article

Bevacizumab plus FOLFOX or FOLFIRI regimens on patients with unresectable liver-only metastases of metastatic colorectal cancer

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Abstract

Background: The present study was aimed to evaluate the efficacy and safety of at least three cycles of Bevacizumab in combination with chemotherapy regimens, FOLFIRI or FOLFOX to treat liver metastatic colorectal cancer and improved response rates in these patients.

Materials and Methods: In this non-randomized clinical trial, 38 patients were enrolled and followed for 12-weeks period of chemotherapy. Fifteen patients under treated with FOLOFX (Group I), 15 patients under treated with FOLOFIRI (Group II), 4 patients under treated with FOLOFX + Bevacizumab (Group III), and 34 patients under treated with FOLOFIRI + Bevacizumab (Group IV). Response to treatment was assessed in all patients as main endpoint. Patients in groups I and II, who did not response to treatment after 12 weeks of chemotherapy, were followed by groups III and IV regimens, respectively, for 12 weeks.

Results: Overall response rate was 35% (19 of 54), and complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) rates in all patients were 18%, 17%, 35%, and 30%. PR, SD, and PD were different among groups, but no statistical significance was noted among groups (*P*-value >0.05). No patient achieved a CR in groups III and IV, although CR was observed in 4 patients (27%) and 6 patients (40%) in groups I and II, respectively. The rare of CR was statistically significant among studied groups (*P*-value = 0.013).

Conclusion: Results showed that adding Bevacizumab to chemotherapy regimens, in patients who did not response to FOLFIRI or FOLFOX regimen, did not increase CR in these patients.

Key Words: Bevacizumab, colorectal cancer, FOLFIRI, FOLFOX, liver metastasis

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INTRODUCTION

Colorectal cancer is the second most deathly cancer worldwide and also is the third and the second most commonly diagn osed cancer in males and females, respectively. It is reported that, in 2008, about 1.2 million new cases and 608,700 deaths have occurred. Though, because of improved treatment and increased awareness and early detection, the mortality rates have been decreasing dramatically in western countries.[1]

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Approximately half of all colorectal cancer patients develop metastatic disease. Liver is the most common site of metastasis and represent the major cause of death in this disease.[2-4] At the time of diagnosis or during the disease course, nearly one-third of patients have liver metastases, whereas depending on the stage of the primary disease, liver metastases occur in 20% to 70% of patients.[5] Surgical resection remains the only treatment that can, to date, ensure long-term survival in 25% to 40% of patients.[6,7] However, because of the location, the size, the number of liver metastases, the residual normal liver, and the extra hepatic disease, 85% of the patients are ineligible to surgery and only 15% of patients are suitable for surgical.[8,9] Palliative chemotherapy increases survival and enhances quality of life when liver metastases are non-resectable.[10]

5FU has been studied more than other drugs for many years, because it represented the only efficacious treatment for advanced colorectal cancer. But, improved success in the treatment of pre-treated or chemo-naive patients have been shown after the introduction of Irinotecan, a topo-isomerase 1 inhibitor, and oxaliplatin, the platinum analog, and combinations of 5-FU with Irinotecan (FOLFIRI) or oxaliplatin (FOLFOX).[11] Also, it is reported that the best treatment results are obtained by FOLFIRI and then FOLFOX, but median survival time still fails to exceed 2 years.

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor, a mediator involved in angiogenesis and, in Europe, is marketed for first-line treatment of metastatic colorectal cancer, in combination with fluorouracil + folinic acid (with or without Irinotecan).[12] Some randomized trials showed that Bevacizumab improved response rates, overall survival, and progression-free survival in colorectal cancer metastatic patients when combined with the different standard chemotherapy regimens.[13,14] Also, Bevacizumab plus standard second-line chemotherapy (FOLFIRI or FOLFOX) is highly active in patients with metastatic colorectal cancer and has an acceptable safety profile.[15]

It is demonstrated that the combination of Bevacizumab plus FOLFOX or FOLFIRI showed modest activity and was relatively tolerable in patients with metastatic colorectal cancer refractory to both FOLFIRI and FOLFOX.[16] Though, authors in another study believed that in practice, there is no evidence that Bevacizumab is any better than current European chemotherapy protocols for first-line treatment of metastatic colorectal cancer.[12] Despite the differences in results of the studies, expansion of the use of neo-adjuvant therapy to include patients with resectable metastatic disease has occurred, but data for such patients is limited, and whether outcomes are improved remains debatable. Therefore, the present study was aimed to evaluate the efficacy and safety of at least three cycles of Bevacizumab combination with chemotherapy regimens, FOLFIRI or FOLFOX to treat liver metastatic colorectal cancer and improved response rates in these patients.

MATERIALS AND METHODS

The present study was performed at the Institute of Oncology, in Sayed Al-Shohada Hospital and some private clinics of oncology in Isfahan, Iran, after it had been approved by Institutional Review Board and Ethics Committee in Isfahan University of Medical Sciences. This was a non-randomized clinical trial, and 38 patients with un-resectable liver metastases from colorectal cancer were enrolled to evaluate the efficacy and safety of at least three cycles of chemotherapy regimens by FOLFIRI and FOLFOX with and without Bevacizumab.

Patients of any gender, older than 18 years old with histopathologically confirmed colorectal adenocarcinoma were eligible if they had a life expectancy of more than 6 months, untreated colorectal liver metastasis that is not amenable to curative resection with measurable lesions, and any extra hepatic metastases or recurrences. Also, patients with asynchronous or metachronous active malignancy; serious co-morbidities such as pulmonary fibrosis or interstitial pneumonia, uncontrollable peptic ulcer disease, upper abdominal intraoperative radiation, history of hepatitis / cirrhosis, concomitant cancers, poorly controlled diabetes mellitus, severe cardiovascular disease (i.e. myocardial infarction, uncontrolled hypertension, uncontrolled arrhythmia) or another serious medical condition; pregnancy or breast-feeding; diarrhea or a peripheral neuropathy greater than grade 1; or a previous history of severe drug-induced allergy were excluded from the study. Before registration, all patients were informed of the investigational nature of the study and provided their written informed consent.

Eligible patients were under treatment by four chemotherapy regimens as followed; in group I, 15 patients, under treatment, using FOLFOX regimen; in group II, 16 patients, under treatment, using FOLFIRI regimen; in group III, 4 patients received FOLFOX regimen plus Bevacizumab; and in group IV, 3 patients received FOLFIRI regimen plus Bevacizumab. Patients in groups I and II after failure of FOLFIRI and FOLFOX were added to groups III and IV, respectively, and treated with Bevacizumab plus FOLFIRI or FOLFOX.

FOLFIRI regimen was administered as followed; CPT-11 at the dose of 200 mgm^{-2} as a 2 h i.v. infusion on day 1; LV was given at the dose of 400 mgm^{-2} as a 2-h i.v. infusion, followed by 5-FU 400 mgm^{-2} as i.v. bolus, and then, 2400 mgm^{-2} as a 22-h continuous i.v. infusion, on days 1 and 2. Also, FOLFOX regimen was administered as followed; oxaliplatin at 85 mg/m^2i.v. over 2 h, day 1 plus LV at 400 mg/m^2i.v. over 2 h on plus 5-FU at 400 mg/m^2i.v. bolus on day 1, then 2400 mg/m^2 continuous infusion over 46-48 h. The Bevacizumab dose was 7.5 mg/kg and was administered i.v. every 2 weeks, initially over 90 min. If the first infusion was well tolerated, the second was delivered over 60 min; if the 60-min infusion was well tolerated, all subsequent infusions were delivered over 30 min.

Data collection included age, sex, primary site, and response to treatment of studied regimens. Response to treatment was assessed in four category included; a complete response (CR) which was defined as the complete disappearance of all assessable disease; a partial response (PR) which was defined as a decrease of ≥30% in the sum of the products of perpendicular dimensions of measurable lesions; progressive disease (PD) which was defined as an increase of >20% in the sum of the products of two dimensions of at least one tumor or the appearance of a new lesion; and stable disease (SD) which was defined as condition of no PR and PD.

The sample size was calculated using the comparison of proportions formula with two-sided log-rank test, $\alpha = 0.05$, and 80% power. All analysis was done by SPSS-20, and data are presented as means ± 1SD or number (%) as appropriate. Age was compared among studied groups by one-way ANOVA. Also, sex, primary site, and response to treatment were compared among studied groups using Chi-square test. Statistical significance was accepted at *P*-value less than 0.05.

RESULTS

Present study was done from January 2012 to January 2013. Of 52 reviewed patients for eligibility, 14 patients were not eligible and did not enter to the study. Thirty-eight patients who were eligible based on studied regimen were followed for 12 weeks. During follow-up, one patient in group II did not desire to continue and was excluded. In groups I and II patients, who did not response to treatment after follow-up period, were treated with groups III and IV regimens repeated every two weeks for three cycles, respectively (nine patients in group I and eight patients in group II) [Figure 1].

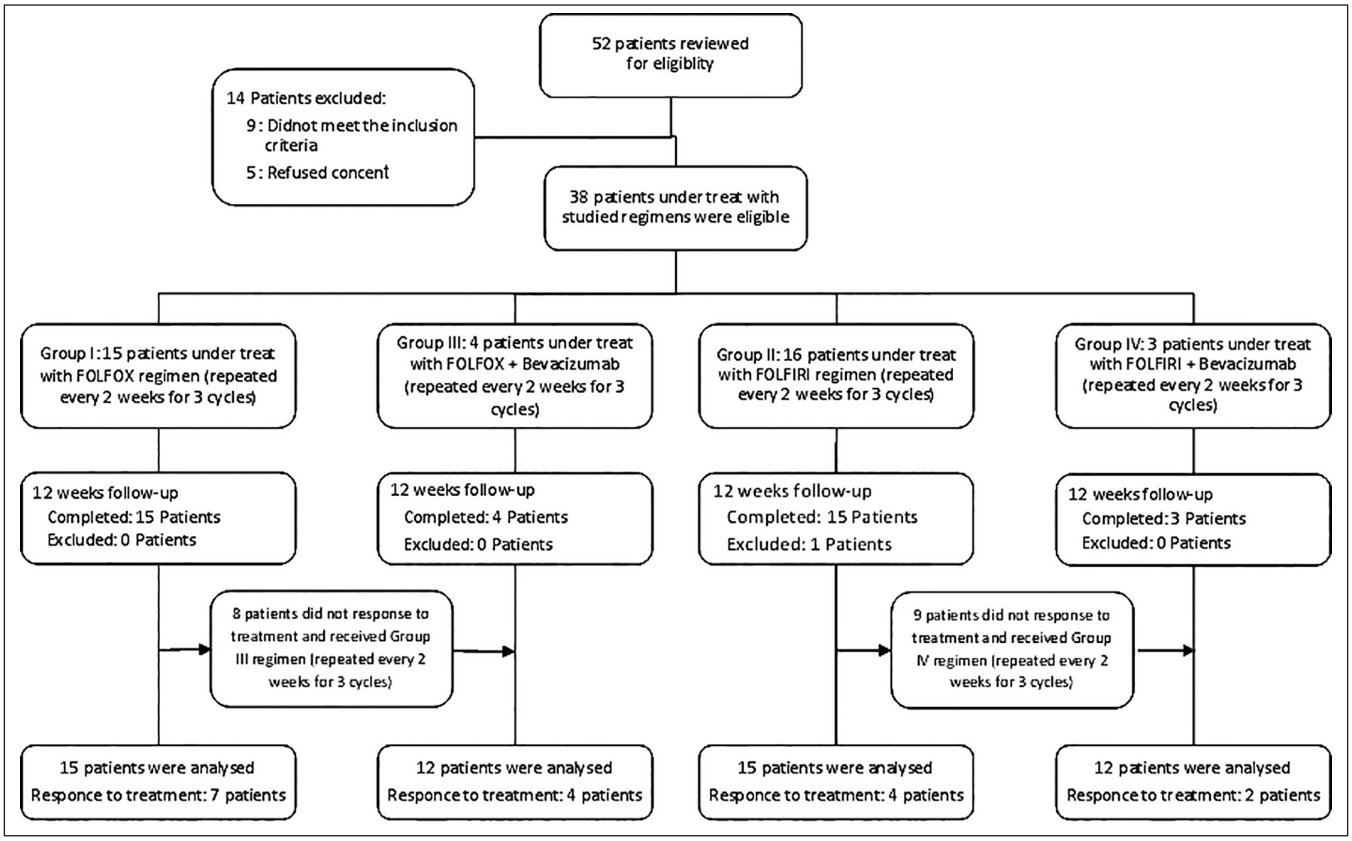

Figure 1: Study flowchart

The mean age of the studied patients was 57.2 ± 12.3 years. Thirty-one patients (56%) were male. Table 1 shows baseline characteristics of studied patients. No significant differences were noted between intervention groups for mean of age and sex combination (*P*-value ≥ 0.5). Colon was found as most of primary site in patients in four studied groups, and there was no significant difference in the frequency of primary site between groups (*P*-value = 0.69).

Response rates to treatment regimens in all studied groups are shown in Table 2. As shown, overall response rate was achieved in 19 of all 54 patients (35%), and CR, PR, SD, and PD rates in all patients were 18%, 17%, 35%, and 30%. Overall response rate in group I was higher than other groups, and in group IV was lower than other groups. But, the difference among groups in the overall response rate to treatment regimens was not statistically significant (*P*-value = 0.42). PR, SD, and PD were different among groups, but no statistical significance was noted among groups (*P*-value > 0.05). No patient achieved a CR in groups III and IV, who received Bevacizumab plus FOLFOX or FOLFIRI, although CR was observed in 4 patients (27%) and 6 patients (40%) in groups I and II, respectively. The rare of CR was statistically significant among studied groups (*P*-value = 0.013).

Table 1: Baseline characteristics of 54 patients with cancer cachexia by group

	Group I	Group II	Group III	Group IV	*P*-value
Age (year)	55.5±10.1	56.6±14.6	57.4±17.3	58.7±16.8	0.65*
Sex					
Male	10 (67)	6 (67)	8 (67)	7 (67)	0.42†
Female	5 (33)	9 (67)	4 (67)	5 (67)	
Primary site					
Colon	12 (80.5)	11 (73)	9 (75)	10 (84)	0.69†
Rectum	2 (13)	4 (27)	3 (25)	1 (8)	
Multiple	1 (6.5)	0	0	1 (8)	

Data expressed as mean ± SD or number (percent), Group I included patients who received FOLFOX regimen every two weeks three times, Group II included patients who received FOLFIRI regimen every two weeks three times, Group III included patients who received FOLFOX regimen plus bevacizumab every two weeks three times, and Group IV included patients who received FOLFIRI regimen plus bevacizumab every two weeks three times, *P*-values calculated by *ANOVA and †Chi-square, *P*-values less than 0.05 were considered to be significant

DISCUSSION

For colorectal cancer, advancements in systemic chemotherapy have improved the clinical response rate and expanded the indications for resection to cases that were previously not operable at the initial visit.[5] This strategy, mentioned to as conversion chemotherapy, is a main reason for the annual rise in the number of liver resections being performed for colorectal liver metastases.[17] It is important to select regimens that offer higher response rates for enabling conversion therapy. The FOLFOX regimen has been shown to be better than FOLFIRI in patients with metastatic colorectal cancer. And, the addition of Bevacizumab to the FOLFOX and FOLFIRI regimens in cases has been suggested to be effective.[18] Therefore, the present study was designed to assess clinical response rate in FOLFOX or FOLFIRI regimens with or without Bevacizumab in patients with colorectal cancer liver metastases. Our results showed that response rate to treatment regimens as main endpoint was different in studied groups, whereas overall response rate in FOLFOX regimen was higher than other regimens, but CR in FOLFOX regimen was higher than other regimens. In FOLFOX or FOLFIRI regimens ± bevacizumab, rate of CR was zero and no patient achieved CR after treatments. It is possible that no achieved CR in FOLFOX and FOLFIRI regimens ± Bevacizumab groups is due to the fact that nine and eight patients in FOLFOX or FOLFIRI groups, respectively, after failure to these regimens were added to Bevacizumab groups and followed for 12 weeks by FOLFOX or FOLFIRI regimens plus bevacizumab.

FOLFOX and FOLFIRI as the two standards chemotherapy regimens are the foundations of modern chemotherapy, and each regimen has positively impacted response rate and survivals.[19] FOLFOX and FOLFIRI regimens were evaluated in many studies, which reported different response rate in studied patients. Several studies reported overall response rate of between 20-50% in patients under treatment with FOLFOX or FOLFIRI regimens,[20-22] Giantonio and colleagues[14] showed that the response rate was

Table 2: Response rate to treatment regimens in all studied groups

	Group I (15)	Group II (15)	Group III (12)	Group IV (12)	*P*-value
Complete response	4 (27)	6 (40)	0	0	0.013
Partial response	3 (20)	0	4 (33)	2 (16)	0.13
Stable disease	5 (33)	6 (40)	3 (25)	5 (42)	0.8
progressive disease	3 (20)	3 (20)	5 (42)	5 (42)	0.39
Overall response rate	7 (47)	6 (40)	4 (33)	2 (16)	0.42

Data expressed as number (percent), Group I included patients who received FOLFOX regimen every two weeks three times, Group II included patients who received FOLFIRI regimen every two weeks three times, Group III included patients who received FOLFOX regimen plus bevacizumab every two weeks three times, and Group IV included patients who received FOLFIRI regimen plus bevacizumab every two weeks three times, *P*-values calculated by Chi-square, *P*-values less than 0.05 were considered to be significant

8.6% in FOLFOX4 regimen, and other studies reported response rate as followed for FOLFOX regimen; OPUS study (phase 2) 37%,[23] NO 16966 study 49%,[24] Tourniguand *et al*. 54%,[25] and Alberts *et al*. 60%.[26] Seventeen percent objective responses were observed in Mabro's study for FOLFIRI regimen,[27] and other studies reported response rate for FOLFIRI regimen as followed; Douillard *et al*. 40.8%,[28] Tourniguand *et al*. 56%,[25] Falcone *et al*. 34%,[29] CRYSTAL study (phase 3) 43%,[30] and Skof *el al*. 48%.[31] As noted, the report of response rate was different between 8.6-60% for FOLFOX or FOLFIRI regimens. Response rate in present study was 47% in FOLFOX and 40% in FOLFIRI regimen, which was similar to most of reported studies, and differences in response rate could be because of the differences in the dose of drugs and number of chemotherapy cycles.

In patients with metastatic colorectal cancer, Bevacizumab usually has been administrated with FOLFIRI or FOLFOX as first-line chemotherapy[32-34] and in randomized trials improved response rates and overall survival when combined with the standard chemotherapy.[35] Bevacizumab, in practice, often hold from the last cycle of preoperative chemotherapy by medical oncologists. In the present study, after combination of Bevacizumab with FOLFIRI and FOLFOX, overall response rate was 25%, and no patient had a CR; also, SD was 33% and PD observed in 42% of studied. Similar to our results, in Kang *et al*. study,[16] 42 patients with metastatic colorectal cancer after failure of FOLFIRI and FOLFOX were treated with Bevacizumab plus FOLFIRI or FOLFOX. Authors showed that 10% of patients had PR and no patient had a CR, giving an overall response rate of 9.5%; also, 52.4% of patients had SD and 31% of patients showed PD. In similar results of these two studies showed that no patient had a CR, but overall response rate in our study was higher than in Kang *et al*. study (25% vs. 9.5%, respectively). The difference between two studies is due to studied patients, whereas, in our study, of 24 studied patients, 17 patients had failure of FOLFIRI or FOLFOX and 7 patients received Bevacizumab with FOLFIRI and FOLFOX as first line, but in Kang *et al*. study, failure of FOLFIRI and FOLFOX was reported in all studied patients. In other study, 53 patients received second-line Bevacizumab plus FOLFIRI (57%), FOLFOX (26%) or other regimens, and overall response rate was 32%.[15] Response rate in the Bev + FOLFOX4 regimen was reported 22.7% in Giantonio *et al*.[14] and in 47% NO 16966 study[24]. Several observational trials confirmed the safety profile of Bevacizumab in first-line of FOLFOX, FOLFIRI regimens.[30,36] As shown, despite of verity in dose and cycles of regimens, response rate in our study is close to other studies and demonstrated that addition of Bevacizumab to FOLFIRI or FOLFOX in first-line of chemotherapy could be more effective.

Present study has several obvious limitations. First, because of study design, patients did not undergo randomization, possibly increasing the risk of selection bias, and the small sample size with only 38 patients was the second limitation of our study. Also, variables like overall survival and adverts effects and toxicity were not measured in the present study. So, further study, however, is needed to clarify and focus on the relatively poor efficacy of addition of Bevacizumab to FOLFIRI or FOLFOX as second-line therapy, adverts effects, and toxicity.

In conclusion, results of the present study showed that adding Bevacizumab to chemotherapy regimens, in patients who did not response to FOLFIRI or FOLFOX regimen, did not increase CR and suggested that addition of Bevacizumab to FOLFIRI or FOLFOX in first-line of chemotherapy may be more effective.

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