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Role of Bevacizumab as Post-Progression Maintenance Therapy in Metastatic Colon Cancer

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Colon cancer is one of the most commonly occurring cancers worldwide, with approximately 50-60% of these patients of metastatic disease and requiring systemic chemotherapy (CTh). Bevacizumab (BVC). The question of whether to continue BVC with the next therapy regimen and the timing of bevacizumab in the overall treatment strategy of advanced metastatic colon cancer-early use (first-line) or later use? awaits further study. Thirty three patients with progressive metastatic colon cancer after first-line therapy were included. Patients were randomized to receive either chemotherapy or combined chemotherapy with bevacizumab. The primary end point was objective response. Secondary end points were median survival, time to tumor progression, toxicity. The median age was 59.7 years (range, 39-70 years), with male/female ratio of 17/16. Partial response with second-line BVC group constituted (25 and 18.8%) in patients with first-line chemotherapy and BVC-based regimen respectively, compared to (11.8 and 5.9%) with second-line chemotherapy (p = 1.01). Median time to progression was (2.3 vs. 4.3 months) for cases with second-line chemotherapy and BVC-based regimens, respectively (p = 0.12). Median survival was (4 vs. 6.7 months) in both groups, respectively (p = 0.22). Grade III/IV of neutropenia occurred in 40, 14.3 and 31.3% in FOLFOX, FOLFIRI and combined BVC-CTh, respectively (p = 0.66). The current trial showed a beneficial effect of re-challenge with Bevacizumab in second line treatment with manageable toxicity profile. Phase III trial is recommended to prove the benefit of continuing treatment with Bevacizumab as maintenance therapy or resuming it after stoppage when progression is documented.

Key words: Second-line therapy, anti-angiogenesis, colonic adenocarcinoma

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INTRODUCTION

Colon cancer is one of the most commonly occurring cancers worldwide, with an incidence of 950,000 per year while approximately 50-60% of these patients are developing metastatic disease and requiring systemic chemotherapy. The treatment of metastatic colon cancer with irinotecan or oxaliplatin in combination with 5-florouracil and folinic acid (leucovorin) and now often in combination with monoclonal antibody antivascular endothelial growth factor (bevacizumab) represents a standard first-line treatment with improved survival among responders. However some patients will not respond satisfactorily to an initial regimen, whereas others may manifest recurrent disease. So, the need for second-line therapy is apparent (Saunders and Iveson, 2006).

Bevacizumab (BVC), a monoclonal antibody directed against vascular endothelial growth factor (VEGF), provides a significant survival advantage (15.6 to 20.3 months) when added to first-line chemotherapy for metastatic colorectal cancer (mCRC). Only a few trials have been conducted using addition of BVC as second-line chemotherapy.

Chen *et al.* (2006) presented results of bevacizumab (Avastin) with 5-florouracil (5-FU) in heavily pretreated patients that resulted in only a 1% response rate. Thus, the benefit of bevacizumab in refractory metastatic disease was unclear. At ASCO (2005), data were presented regarding the use of bevacizumab in second/third line therapy in combination with oxaliplatin-based chemotherapy (FOLFOX). Giantonio *et al.* (2007) in ECOG 3200 studied the addition of BVC with second-line therapy for patients with progressive mCRC after 5-FU and irinotecan. It was reported that response rates were improved by 10% and BVC monotherapy was inferior to both other arms of mono-chemotherapy and combined BVC-chemotherapy. Thus, the question of whether to continue BVC with the next therapy regimen awaits further study. The other important clinical implication relates to the timing of bevacizumab in the overall treatment strategy of advanced metastatic colon cancer- early use (first-line) or later use?

The objective of this study is was to assess the role of BVC as a maintenance second-line therapy and to estimate the effect of previous first-line anti-angiogenic BVC therapy on pattern of tumor relapse, survival and response to further post-progression treatment.

PATIENTS AND METHODS

Study design: A phase II randomized study was performed according to the guidelines of good clinical practice and after given written informed consent prior to treatment. Thirty three patients from March, 2005 to May, 2007 form multiple oncology centers in Saudi Kingdom with metastatic colon cancer and tumor progressions after previous first-line therapy were entered onto the study. Cases with tumor progression after first-line therapy of 5-florouracil, oxaliplatin/irinotecan based regimens with or without anti-angiogenic treatment (bevacizumab) were included. Patients were randomized to receive either chemotherapy or combined chemotherapy with bevacizumab. The primary end point was objective response. Secondary end points were median survival, time to tumor progression, toxicity.

Inclusion criteria:

- Histologically confirmed metastatic colon cancer
- At least 2 months after prior palliative surgery and recovered
- At least 2 months after previous chemotherapy including 5-Florouracil, leucovorin, oxaliplatin/ irinotecan based regimens with or without anti-angiogenic treatment (bevacizumab) or radiotherapy
- Measurable disease, defined as ≥1 unidimensionally measurable lesion ≥20 mm by conventional techniques or; ≥10 mm by spiral CT scan
- Age 18 to 70 years old
- Eastern Cooperative Oncology Group performance status 0-2
- Adequate bone marrow function: WBCs >4,000 μL^{-1}, absolute neutrophil count >2,000 μL^{-1} and platelets >100,000 μL^{-1}
- Adequate renal function: creatinine <1 ×upper normal limit (UNL) or creatinine clearance ≥60 mL min^{-1}
- Adequate hepatic function: bilirubin <1.5×UNL, AST/ALT levels <2.5×UNL and alkaline phosphatase <5×UNL (except in case of bone metastasis without any liver disease)

Exclusion criteria:

- Contraindication to any drug contained in the chemotherapy regimen
- Other tumor type than adenocarcinoma
- Presence or history of CNS metastasis
- Bowel obstruction, serious gastro-intestinal bleeding, or abdominal fistula within six months
- Presence of pretreatment proteinuria (≥grade 2)
- History of severe thrombo-embolic events
- Non-healing wound, ulcer or bone fracture

- Peripheral neuropathy > grade I
- History of significant neurological or psychiatric disorders
- Pregnant or lactating women
- Clinically significant cardiac disease (e.g., severe non-compensated hypertension, non-compensated heart failure, dilated cardiomyopathy and coronary heart disease with ST segment depression in ECG) or myocardial infarction within the last 6 months
- Serious pulmonary conditions/illness (e.g., chronic lung disease with hypoxemia)
- Serious metabolic disease such as severe non-compensated diabetes mellitus
- Serious uncontrolled recurrent infections or other serious uncontrolled concomitant disease

Treatment: Cases with previous disease progression on first-line irinotecan-based regimen (FOLFIRI) were to receive second-line oxaliplatin-based regimen (FOLFOX) with or without bevacizumab. The reverse sequence was applied; those with previous disease progression on 1st line FOLFOX were to receive 2nd line FOLFIRI regimen with or without bevacizumab. FOLFOX6 regimen was given as oxaliplatin 100 mg m^{-2} IV over 2 h day 1, folinic acid 400 mg m^{-2} IV over 2 h on day 1, bolus of 5-florouracil 400 mg m^{-2} IV and 46 h infusion of 5-florouracil 2400 mg m^{-2} day 1. FOLFIRI regimen consisted of irinotecan 180 mg m^{-2} IV over 1.5 h day 1, folinic acid 400 mg m^{-2} IV over 2 h on day 1, bolus of 5-florouracil 400 mg m^{-2} IV and 46 h infusion of 5-florouracil 2400 mg m^{-2} day 1. Bevacizumab was given at dose of 5 mg kg^{-1} over 1 h every 2 weeks. Anti-emetic treatment consisted of an antiserotonin agent plus dexamethasone in a 15 min at dose of 5 mg kg^{-1} infusion before starting chemotherapy. In addition, premedication with oral prednisone was used for prophylaxis of chemotherapy-induced hypersensitivity and fluid retention. GM-CSF 5 μg/kg/day subcutaneously was given on days 2, 3 and 4 of each cycle. Treatment was postponed by a maximum of 2 weeks if the absolute neutrophil count was <1500 μL^{-1} or the platelet count was <100,000 μL^{-1}. A 25% drug dose reduction was planned in case of grade 4 neutropenic fever (absolute granulocyte count <500 μL^{-1} at the time of a documented temperature of 38°C or higher), as well as in case of grade 4 mucositis or grade 3 neurotoxicity. Cycles were repeated every 2 weeks for a maximum of 6 cycles and were discontinued in case of unacceptable toxicity, treatment delay longer than 2 weeks, disease progression or patient refusal.

Pretreatment and follow-up studies: Pretreatment evaluation included clinical history and physical examination, complete blood cell count, biochemical profile, tumor markers Carcino Embryonic Antigen (CEA), lactate dehydrogenase (LDH), Computed Tomography (CT) of thorax, abdomen and pelvis, ECG and resting Left Ventricular Ejection Fraction (LVEF) determination by echocardiography. Blood counts were obtained on days 1, 7, 13 and 20; biochemical profile was repeated every 4 weeks. All measurable parameters of disease were re-evaluated every 6 weeks, until the tumor progressed. Cardiac monitoring was performed at baseline with ECG repeated every cycle and LVEF after fourth cycle.

Evaluation of response and toxicity: Patients were evaluated for response to chemotherapy every three cycles of treatment. The best objective imaging technique for the particular patient was selected from the pretreatment evaluation by CT scan and tumor response was assessed together with an independent radiologist. The standard Response Evaluation Criteria In Solid Tumors (RECIST) were used to evaluate clinical response (Therasse *et al*., 2000). Median Time to Tumor Progression (TTP) and median Overall Survival (OS) were calculated starting from the date of treatment to the date of disease progression, death or last follow-up evaluation. Toxicity was assessed in each treatment cycle of therapy using the National Cancer Institute Common Toxicity Criteria (version 2.0). Patients, who received at least one cycle of treatment were considered assessable for response and toxicity. Patients, who developed rapid tumor progression after any amount of therapy also were evaluated. Data for tumor response are based on an intent-to-treat analysis.

Statistical considerations: The primary end point was to estimate the treatment response rate with Fisher's exact test. Secondary end points were TTP, OS and safety. The statistical analysis was made using the Statistical Product and Service Solutions, SPSS 10.0 for Windows. Univariate analysis was performed using General Linear Model. Time to tumor progression and survival was determined using the Kaplan-Meier method, Cox regression analysis and the log-rank test was used to assess statistical differences between groups. As multiple statistical testing was performed, a two-sided p-value of less than 0.05 was considered significant and 95% CIs were quoted.

RESULTS

Thirty three patients from March, 2005 to May, 2007 with metastatic colon cancer with tumor progression after previous first-line therapy were entered onto the study. Seventeen patients had progression on previous

chemotherapy and sixteen cases had progression on combined chemotherapy and bevacizumab. Cases with previous progression on 1st line therapy (BVC-naïve or BVC-based) were stratified according to second-line treatment into two groups; 17 patients of second-line chemotherapy and 16 cases of combined chemotherapy with bevacizumab. All patients were evaluable for response and toxicity.

Patients' characteristics in (Table 1) showed well-balanced data at baseline with no statistically significant difference between treatment groups. Median age of total cases was 59.7 years (range, 39-70 years) with 46.3% of cases <60 years and 53.7% of cases were more than 60 years. Male/female ratio was 17/16. ECOG performance status (2) constituted 48.5% of cases. Each of well and poor differentiated adenocarcinoma constituted 45.5% and 42.4% compared to mucinous carcinoma with 12.1% of cases. Low tumor bulk with one metastatic tumor site was present in 13 patients (39.4%) of total cases. High tumor burden with more than one site of metastatic lesions was present in 20 patients (60.6%) of total cases as shown in (Table 1). Elevated levels of LDH (>230 mg dL^{-1}) and high levels of CEA (more than 5000 ng mL^{-1}) were present in 48.5 and 21.2% of total cases, respectively.

Thirty three patients received a total of 136 cycles. Median chemotherapy cycles per patient was 4 (range, 2-8 cycles). Nine out of 17 cases (52.9%) with disease progression after front-line chemotherapy group and 5/16 (31.3%) of progression with front-line combined chemotherapy-bevacizumab group had completed scheduled number of 6 cycles. Four and three patients of both groups respectively received additional 2 cycles to complete 8 cycles. Table 2 showed the response to different types of second-line treatment (chemotherapy and combined bevacizumab with chemotherapy) after stratification of patients according to previous first-line therapy (chemotherapy vs. bevacizumab) arms. Partial response with second-line B VC group constituted (25%; 95% CI; 18.1-32.2%) and (18.8%; 95% CI; 12.5-25.2%) in patients with first-line chemotherapy and BVC-based regimen respectively, compared to (11.8%; 95% CI; 5.1-17.9%) and (5.9%; 95% CI; 3.1-8.8%) with second-line chemotherapy respectively (p = 1.01). Disease control (partial response and stationary disease) was higher in BVC-based second-line treatment as compared to second-line chemotherapy alone in patients with disease progression on front-line therapy either chemotherapy alone or combined chemotherapy with bevacizumab (Table 2).

Disease progression on second-line BVC-based treatment was lower than second-line chemotherapy alone (p = 0.8) as shown in (Table 2). Disease progression on second-line BVC-based treatment occurred in (12.2%; 95% CI; 8.3-16.4%) and (6.3%; 95% CI; 2.7-10.9%) of patients of first-line chemotherapy and BVC-based

Table 1: Baseline characteristics of 33 patients with metastatic colon cancer

		Post-progression second-line treatment		
Patient characteristics	Total (33 cases) (%)	CTh (17 cases) (%)	CTh+BVC (16 cases) (%)	p-value
Median age (years)	59.7	61.5	57	--
Gender				
Female	(16) 48.5	(9) 52.9	(7) 43.8	0.73
Male	(17) 51.5	(8) 47.1	(9) 56.2	
PS				
0-1	(17) 51.5	(8) 47.1	(9) 56.2	0.73
2	(16) 48.5	(9) 52.9	(7) 43.8	
Pathology				
Well-differentiated	(15) 45.5	(8) 47.1	(7) 43.8	0.63
Poor-differentiated	(14) 42.4	(6) 35.3	(8) 50	
Mucinous carcinoma	(4) 12.1	(3) 17.6	(1) 6.3	
Tumor bulk				
Low (1 metastatic site)	(13) 39.4	(8) 47.1	(5) 31.3	0.48
High (>1 metastatic site)	(20) 60.6	(9) 52.9	(11) 68.8	
LDH				
Normal	(17) 51.5	(7) 41.2	(10) 62.5	0.30
Elevated	(16) 48.5	(10) 58.8	(6) 37.5	
CEA (ng mL^{-1})				
<500	(6) 18.2	(2) 11.8	(4) 25	0.05
501-1000	(14) 42.4	(7) 41.2	(7) 43.8	
1001-5000	(6) 18.2	(6) 35.3	--	
>5000	(7) 21.2	(2) 11.8	(5) 31.3	
Front-line treatment				
CTh (17 cases)	(17) 51.5	(8) 47.1	(9) 56.3	0.73
CTh+BVC (16 cases)	(16) 48.5	(9) 52.9	(7) 43.8	

CTh: Chemotherapy, BVC: Bevacizumab, PS: Performance status, LDH: Lactate dehydrogenase, CEA: Carcino-Embryonic Antigen,

Table 2: Second-line treatment response in relation to front-line treatment in 33 patients with metastatic colon cancer

		Post-progression 2nd-line treatment			
Response	Front-line treatment	Total cases (33 cases) (%)	CTh (17 cases) (%)	CTh + BVC (16 cases) (%)	p-value
PR	CTh	(6) 18.2	(2) 11.8	(4) 25.0	
	CTh+BVC	(4) 12.1	(1) 5.90	(3) 18.8	1.01
SD	CTh	(5) 15.2	(2) 11.8	(3) 18.8	
	CTh+BVC	(5) 15.2	(2) 11.8	(3) 18.8	1.00
DP	CTh	(6) 18.2	(4) 23.5	(2) 12.2	
	CTh+BVC	(7) 21.2	(6) 35.3	(1) 6.30	0.56

CTh: Chemotherapy, BVC: Bevacizumab, PR: Partial Response, SD: Stationary Disease, DP: Disease Progression

Table 3: Survival and time to tumor progression after second-line treatment

	Post-progression 2nd-line treatment		
Outcome	CTh (17 cases)	CTh + BVC (16 cases)	p-value
TTP	2.3 ms (95% CI; 0.8- 3.8)	4.3 ms (95% CI; 2.5- 6.1)	0.12
OS	4 ms (95% CI; 2.4- 5.6)	6.7 ms (95% CI; 3- 10.4)	0.22

CTh: Chemotherapy, BVC: Bevacizumab, TTP: median time to progression, OS: median survival, ms: Months, CI: 95% Confidence interval, ms: Months, $p<0.05$ (Log. rank significance)

regimen, compared to (23.5%; 95% CI; 18.1-28.9%) and (35.3; 95% CI; 27.1-43.3%) with second-line chemotherapy alone, respectively.

Treatment outcome including median survival and median time to disease progression in relation to second-line therapy was presented in Table 3 and Fig. 1. With a median period of follow up of 8.5 months (0.1-11.2 months), current study results showed that addition of bevacizumab to chemotherapy in second-line treatment had higher TTP (4.3 vs. 2.3 months) in chemotherapy arm ($p = 0.12$) and higher OS (6.7 months) in combined BVC- chemotherapy compared to (4 months) in chemotherapy arm ($p = 0.22$) as shown in Table 3 and Fig. 1.

Treatment outcome of 2nd line treatment in relation to previous front-line therapy was shown in Table 4 and Fig. 2 and 3. Median time to disease progression and median survival was higher in first-line bevacizumab-naïve patients (previously treated with first-line chemotherapy alone) compared to cases of first-line BVC-based therapy in all cases of post-progression 2nd line treatment groups (chemotherapy or combined BVC with chemotherapy) (Table 4).

Median time to progression in 2nd line BVC-based therapy was higher in BVC-naïve 1st line treatment (4.9 months) compared to 4.1 months in BVC-based 1st line treatment ($p = 0.06$) as shown in Table 4 and Fig. 2. Median survival in 2nd line BVC-based therapy was significantly higher in BVC-naïve 1st line treatment (9.1 months) compared to BVC-based 1st line treatment (6.3 months) with ($p = 0.018$) as shown in Table 4 and Fig. 3.

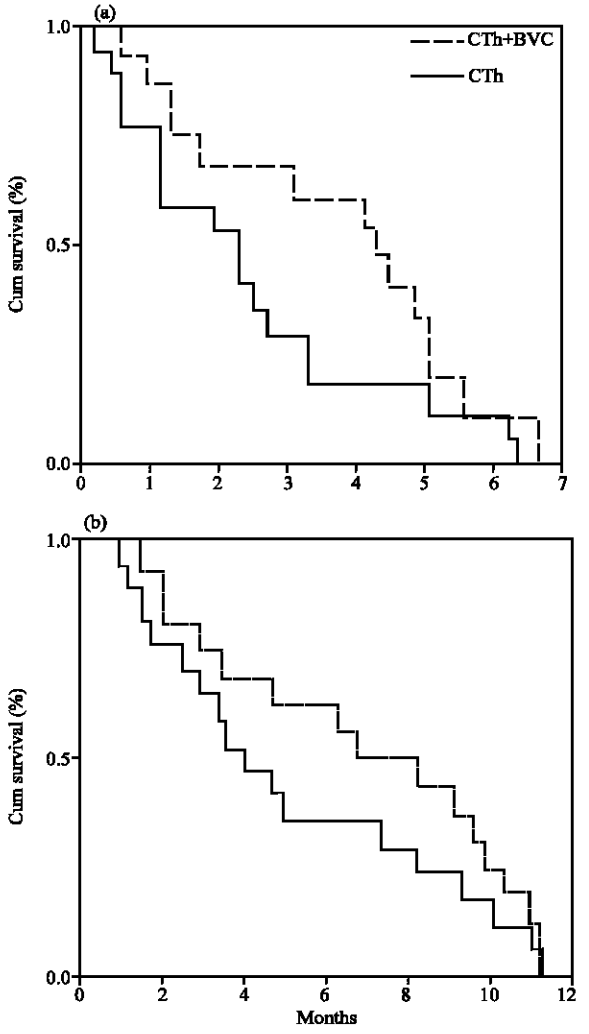

Fig. 1: Kaplan Meier curves of time to progression and survival according to second-line treatment, (a) Median time to progression in relation to second line treatment and (b) Median survival in relation to second line treatment

Univariate and Cox regression analysis of different prognostic factors for median survival and median time to tumor progression was presented in Table 5. Univariate

Table 4: Survival and time to tumor progression after second-line treatment in relation to first-line therapy

Outcomes	Front-line treatment	Post-progression 2nd-line treatment: CTh (17 cases)	Post-progression 2nd-line treatment: CTh+BVC (16 cases)	p-value
TTP	CTh (17 cases)	2.3 ms (95% CI; 0.1-5.3)	4.9 ms (95% CI; 0.1- 10.2)	0.06
	CTh+BVC (16 cases)	1.9 ms (95% CI; 0.1-3.9)	4.1 ms (95% CI; 1- 7.2)	
OS	CTh (17 cases)	7.4 ms (95% CI; 0.1-16.4)	9.1 ms (95% CI; 6.5- 11.7)	0.018*
	CTh+BVC (16 cases)	3.5 ms (95% CI; 3.2- 3.8)	6.3 ms (95% CI; 0.1- 13.7)	

CTh: Chemotherapy, BVC: Bevacizumab, TTP: median time to progression, OS: median survival, ms: months, CI: 95% Confidence interval, ms: months, *p<0.05 (Log. rank significance)

analysis of (age, gender, performance status, LDH, CEA levels, tumor bulk, pathology, first-line therapy and post-progression 2nd line treatment) revealed that performance status, type of pathology and CEA levels had significant value in relation to median time to progression, while performance status, pathological type and post-progression treatment had significant effect on median survival as shown in Table 5.

However, analyzing these factors with Cox regression analysis revealed significant p-values of 0.001, 0.01, 0.006, 0.002 and 0.04 for performance status, pathological type, LDH, elevated CEA levels and post-progression second line treatment respectively in relation to median time to

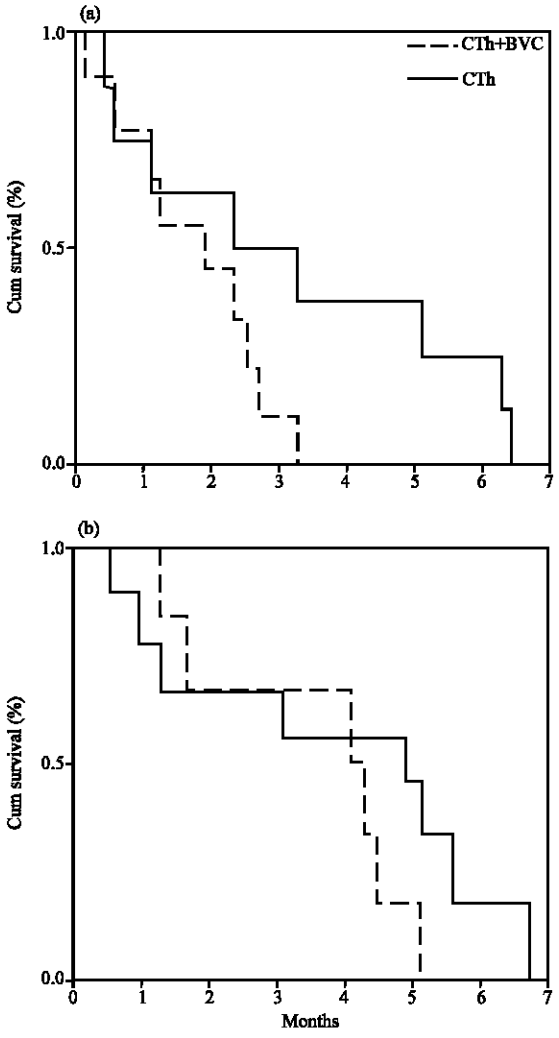

Fig. 2: Survival curves for time to progression after second-line treatment in relation to first-line treatment, (a) Median time to progression for 2nd-line chemotherapy in relation to 1st-line treatment and (b) Median time to progression for 2nd line CTh+BVC in relation to 1st-line treatment

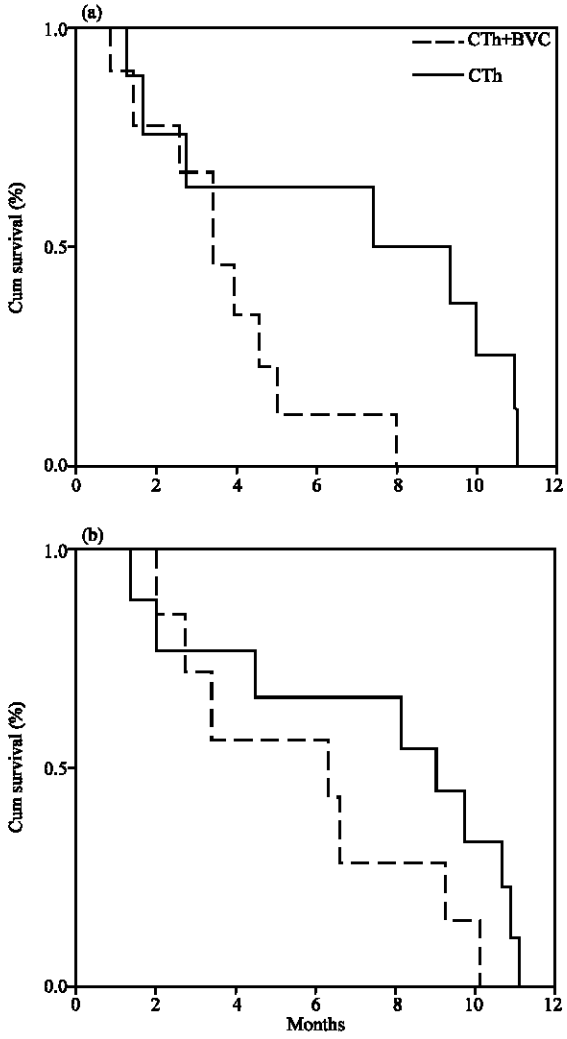

Fig. 3: Kaplan Meier curves of survival for second-line treatment in relation to first-line treatment, (a) Median survival for 2nd line chemotherapy in relation to 1st line treatment and (b) Median survival for 2nd line CTh+BVC in relation to 1st line treatment

Table 5: Univariate and Cox regression analysis of different prognostic factors for median survival and median time to tumor progression

	p-value			
	Univariate analysis		Cox regression	
Prognostic factors	TTP	OS	TTP	OS
Median age (years)	0.22	0.46	0.62	0.28
Gender				
Female				
Male	0.58	0.86	0.44	0.68
PS				
0-1				
2	0.005*	0.005*	0.001*	0.001*
Pathology				
Well-differentiated				
Poor-differentiated	0.011*	0.001*	0.01*	0.001*
Mucinous carcinoma				
Tumor bulk				
Low (1 metastatic site)	0.42	0.18	0.49	0.69
High (>1 metastatic site)				
LDH				
Normal				
Elevated	0.11	0.44	0.006*	0.02*
CEA (ng mL^{-1})				
<500				
501-1000				
1001-5000	0.001*	0.06	0.002*	0.007*
>5000				
First-line treatment				
CTh (17 cases)	0.63	0.08	0.53	0.06
CTh+BVC (16 cases)				
Post-progression 2nd-line				
CTh (17 cases)	0.13	0.038	0.04*	0.20
CTh+BVC (16 cases)				

CTh: Chemotherapy, BVC: Bevacizumab, PS: Performance status, LDH: Lactate dehydrogenase, CEA: Carcino-Embryonic Antigen, TTP: Median time to progression, OS: Median survival, *p<0.05

progression, while performance status, pathological type, LDH and CEA levels had significant effect on median survival (p = 0.001, 0.001, 0.02 and 0.007, respectively) as presented in Table 5.

Grade III/IV toxicity of FOLFOX, FOLFIRI and combined BVC-CTh was presented in Table 6. Grade III/IV of neutropenia was higher in FOLFOX and combined BVC-CTh (40 and 31.3%) compared to 14.3% FOLFIRI cases respectively (p = 0.66). Grade III/IV diarrhea was higher in FOLFIRI group as constituted 28.6% compared to 10 and 18.8% in FOLFOX and combined BVC-CTh regimen respectively (p = 0.64).

However neuropathy of grade III/IV was higher in FOLFOX and combined BVC-CTh groups as constituted 40 and 37.5% compared to 14.3% in FOLFIRI patients respectively (p = 0.54). Grade III/IV alopecia had highest incidence in FOLFIRI cases as constituted 42.9% compared to 0 and 12.5% in FOLFOX and combined BVC-CTh groups, respectively (p = 0.51). Vascular toxicity with ischemic events, hypertension and bleeding occurred only in combined BVC-CTh group in 6.3, 12.5 and 6.3% respectively with no statistical significance difference. There were no treatment-related deaths.

Table 6: Grade III and IV toxicity in different second-line treatment groups

	Second-line treatment						
	FOLFOX		FOLFIRI		BVC+CTh		
Grade III and IV toxicity	(10 cases)	(%)	(7 cases)	(%)	(16 cases)	(%)	p-value
Anemia	1	10	--		5	31.3	0.75
Neutropenia	4	40	1	14.3	5	31.3	0.66
Thrombocytopenia	2	10	1	14.3	1	6.3	0.85
Nausea, vomiting	2	20	2	28.6	3	18.8	0.64
Mucositis	1	10	2	28.6	2	12.5	0.73
Diarrhea	1	10	2	28.6	3	18.8	0.64
Fatigue	2	20	1	14.3	3	18.8	0.35
Neuropathy	4	40	1	14.3	6	37.5	0.54
Hand and foot syndrome	1	10	---		1	6.3	0.61
Allergic reaction	2	20	---		1	6.3	0.35
Alopecia	---		3	42.9	2	12.5	0.51
Vascular, ischemia	---		---		1	6.3	1.0
Hypertension	---		---		2	12.5	1.0
Bleeding	---		---		1	6.3	1.0

CTh: Chemotherapy, BVC: Bevacizumab, FOLFOX: Oxaliplatin-based chemotherapy, FOLFIRI: Irinotecan-based chemotherapy

Table 7: Cost of chemotherapy treatment in (Egyptian pounds)

Cost of one cycle of	Egyptian pounds
Irinotecan-based chemotherapy	3,260±170
Oxaliplatin-based chemotherapy	4,510±130
Irinotecan-based chemotherapy+Bevacizumab	13,710±270
Oxaliplatin-based chemotherapy+Bevacizumab	14,860±310

(1 Egyptian pound = 0.18 American dollars)

Average cost of treatment in Egyptian pounds, (1 Egyptian Pound = 0.18 American dollars) was shown in Table 7. The cost was 13,710±270 and 14,860±310 pounds in BVC-based chemotherapy with irinotecan and oxaliplatin respectively.

DISCUSSION

The study showed that addition of bevacizumab in second-line chemotherapy had higher disease control (partial response and stable disease), median time to progression and median survival in bevacizumab-naïve patients (previously treated with first-line chemotherapy alone) compared to those previously treated with first-line BVC-based therapy. However, those with discontinuation of 1st line combined BVC and chemotherapy after disease progression had significantly lower median time to disease progression and median survival than patients with first-line chemotherapy.

Results of current study are consistent with GERCOR study by Tournigand *et al.* (2004) as overall response and median time to progression was 11.8% and 2.3 months in second-line chemotherapy, respectively.

Addition of bevacizumab to chemotherapy in second-line treatment had higher TTP and OS (4.3 and 6.7 months) compared to (2.3 and 4 months) in chemotherapy group respectively, which was consistent with ECOG E3200 trial by Giantonio *et al.* (2007) who reported a positive survival

advantage with the addition of bevacizumab to 2nd line chemotherapy, however current study showed no statistical significance difference. Added to that; ECOG 3200 excluded patients who received prior BVC. So, it did not address the second-line use of BVC after failure of BVC-containing regimens.

However, analysis of current study data after stratification of patients according to previous 1st line therapy showed higher TTP and median survival in BVC-naïve cases and lower TTP, OS in combined 1st line BVC-chemotherapy patients with statistical significant difference in survival ($p = 0.018$) which reflected that the discontinuation of 1st line BVC leads to more tendency for tumor progression that could be explained by the fact that BVC targets and binds to Vascular Endothelial Growth Factor to inhibit stimulation of growth and formation of new blood vessels. So, if BVC was discontinued, VEGF would be released from suppression of BVC that leads to more neo-vascularization, more growth of tumor vasculature with more disease progression. So, it was recommended not to discontinue BVC even for patients who progressed on front-line combined BVC with chemotherapy, otherwise; there will be more aggressive disseminated tumor progression with very high levels of CEA.

The sample size of current study was relatively small as several patients after tumor progression on front-line treatment were either unfit or refusing any further treatments. Despite the weakness with relatively small sample size, the study is scientifically important and clinically relevant. As it showed increases in progression-free and overall survival in second-line BVC containing regimen especially for 1st line BVC-naïve cases. The suspected mechanism of action of bevacizumab suggests that patients as long as tolerating BVC should be maintained on it, but other factors (including cost and side effects) must be considered. This augments the suggestion of preserving BVC for second/third line of palliative treatment in mCRC after failure of other multiple treatment options is preferable than discontinuation of BVC in first-line treatment.

Partial response in 2nd line BVC-based treatment was higher in 1st line BVC-naïve cases with discrepancy between activity (response rate) and efficacy (overall survival) in current study which is consistent with Kabbinavar *et al.* (2005) and Hurwitz *et al.* (2004) as both studies suggested that there may be an independent effect of bevacizumab from chemotherapy.

Performance status, type of pathology, LDH and CEA levels had statistical significant effect on median time to progression and median survival which is in contrast to Kabbinavar *et al.* (2005) and Hurwitz *et al.* (2004) who reported that there is independence of the beneficial effects from prognostic factors (except for serum albumin).

Alopecia, diarrhea, mucositis and vomiting were the most common non-hematological toxicities in irinotecan regimen. Grade III/IV of hematological toxicity (leukopenia), neurotoxicity was encountered in 40% of cases in oxaliplatin-based regimen. Grade III/IV of vascular and ischemic events, hypertension and bleeding occurred relatively lower than 15% of cases which are consistent with (Giantonio *et al.*, 2007).

Grade 3-4 hematological toxicity occurred in 21 cycles (15.4% of total cycles) and generally between 2nd to 6th cycles. Febrile neutropenia was successfully treated with GM-CSF and broad-spectrum antibiotics. The duration of neutropenia and thrombocytopenia was usually <7 days. Recovery to normal at time of the subsequent planned infusion was experienced in majority of cases. The full recommended dose could not be administered on consecutive cycles as planned, because of frequency, severity and duration of neutropenia imposed multiple treatment delays and/or 25% dose reductions in a total of 7 cycles in FOLFOX regimen. These toxicities were still tolerable and acceptable. There were no treatment-related deaths in the study.

Given the high cost of bevacizumab, selection of patients for maximum benefit on activity (response rate) and efficacy (overall survival) was recommended. Bevacizumab is advised to be maintained in the second- and third-line settings. Selection of patients for bevacizumab was recommended with taking into consideration the cost-benefit value and that the discontinuation of BVC would increase tumor progression.

CONCLUSION

Current trial showed that post-progression addition of bevacizumab with chemotherapy had higher disease control (partial response and stable disease), time to progression and survival in bevacizumab-naïve patients compared to those previously treated with first-line BVC-based therapy. There is a beneficial effect of re-challenge with Bevacizumab in second line treatment with manageable toxicity profile. Phase III trial is recommended to prove the benefit of continuing treatment with Bevacizumab as maintenance therapy or resuming it after stoppage when progression is documented.

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