Med. J. Cairo Univ., Vol. 86, No. 7, December: 3743-3751, 2018
www.medicaljournalofcairouniversity.net

Phase II Randomized Trial of Biweekly Bevacizumab, Capecitabine, Oxaliplatin and Irinotecan (BEV- CAPEOXIRI) Versus Triweekly Bevacizumab, Capecitabine and Oxaliplatin (BEV- CAPEOX) in Metastatic Colon Carcinoma

ALI ABD EL-ALEEM ALI, M.D.* and MAHMOUD ABUL-MAKAREM, M.D.**

The Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Ain Shams University and The Department of General Surgery, Faculty of Medicine, Al-Azhar University***

Abstract

Background: Bevacizumab, Capecitabine and Oxaliplatin (BEV-CAPEOX) is an effective combination in patients with Metastatic Colon Carcinoma (MCC). Irinotecan is also an active agent in those patients.

Aim of the Study: To compare toxicity and efficacy of first-line BEV-CAPEOXIRI (consisting of modified biweekly schedule of BEV-CAPEOX plus irinotecan) with BEV-CAPEOX.

Patients and Methods: A total of 65 patients with MCC who are chemo naïve were randomized into 2 groups. Group 1 (n=33) received BEV-CAPEOXIRI and Group 2 (n=32) BEV-CAPEOX.

Results: The incidence of grade 3-4 neutropenia, febrile neutropenia and G3-4 diarrhea were higher in BEV-CAPEOXIRI arm (12% versus 0%, 9% vs. 0% and 18% vs. 3%, respectively) while peripheral neuropathy G1-2 & G3 were higher in BEV-CAPEOX arm (41% & 9% vs. 18% & 3%, respectively) and also higher palmar plantar erythrodysaesthesia G1-2 (38% vs. 21%). On comparing BEV-CAPEOXIRI with BEV-CAPEOX: Partial remission was observed in 82% vs. 69% of patients, progressive disease in 9% vs. 22% of patients, respectively while 9% of patients in each group had stable disease. Median Progression Free Survival (PFS) was 15 months (95% CI; 14-16) vs. 12 months (95% CI; 11-13), respectively, p=0.01. Median Overall Survival (OS) was 26 months (95% CI; 25-27) vs. 24 months (95% CI; 23, 25), respectively, p=0.02.

Conclusion: In comparison to BEV-CAPEOX, first-line BEV-CAPEOXIRI is more effective with a higher response rate, median PFS/OS, lower neurotoxicity, lower palmar plantar erythrodysaesthesia but higher manageable diarrhea and neutropenia.

Key Words: *Metastatic colon cancer – Capecitabine – Oxaliplatin – Irinotecan – Bevacizumab.*

Correspondence to: Dr. Ali Abd El-Aleem Ali, The Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Ain Shams University

Introduction

COLON carcinoma is the third common cause of death from cancer [1]. Approximately, 60 per cent of patients present with metastatic disease [2,3]. The outcome of treatment of metastatic colon carcinoma is not yet convenient and there is need for more effective regimens. Several studies have shown that prognosis is poor with median Overall Survival (OS) ranging from 11 to 18 months [4,5].

Fluoropyrimidine in form of fluorouracil or capecitapine in combination with oxaliplatin or irinotecan and in addition to a targeted therapy as bevacizumab represent the common combination as frontline treatment of metastatic colon carcinoma. In case of wild KRAS and NRAS status, panitumumab or cetuximab can be used instead of bevacizumab [6-8].

The use of capecitabine instead of 5-FU, either with irinotecan or oxaliplatin, was proved to be of equivalent effect [9,10].

Capecitabine represents a more convenient and easier treatment replacing 5-fluorouracil that needs about 48 hours infusion usually administered through central venous line [11]. The substitution of capecitabine for the infusion of 5-FU decreases the complications associated with the central venous catheter which is needed in the FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) or FOLFOXIRI (FOLFOX plus irinotecan) regimens [12].

Toxicity of capecitabine is variable between world regions. There are different grades of palmar plantar erythrodysaetheisia (hand and foot syn-

drome) or diarrhea at same doses. It is less pronounced in Europe and Asian countries in comparison to USA. Common schedule in Europe and Asia is capecitabine 1000mg/m^2 on days 1 to 14 every 21 days but in USA 850mg/m^2 twice daily for 14 days every 21 days [13,14].

Several randomized trials showed that XELOX (capecitabine plus oxaliplatin) achieved similar treatment outcome as FOLFOX4 or FOLFOX6 in metastatic colorectal cancer [15-18].

Fuchs et al., [19] reported the phase III BICC-C trial, which compared three different protocols: Irinotecan plus fluorouracil infusion (FOLFIRI), irinotecan plus bolus FU (modified IFL) and capecitabine plus irinotecan (XELIRI) which included (capecitabine 1000mg/m^2 twice daily, on days 1 to 14 of every 21 days plus irinotecan 250 mg/m^2 on day 1). FOLFIRI had more favorable efficacy and toxicity. In comparison to FOLFIRI: XELIRI was associated with higher rates of G3-4 diarrhea (48 versus 14%).

However, a meta-analysis of 6 randomized trials compared capecitabine in combination with irinotecan (XILIRI) to fluorouracil-leucovorin infusion plus irinotecan (FOLFIRI) including the above trial (BICC-C trial) and concluded that XILIRI had equivalent efficacy and toxicity [20].

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor-A. It adds at least a modest overall and progression free survival benefit when added to FOLFOX or FOLFIRI regimens for metastatic colorectal cancer [21,22].

The TRIBE randomized trial compared FOLFOXIRI versus FOLFIRI, combining each with bevacizumab. Median OS was 29.8 (95%CI 26.0-34.3) vs. 25.8 (95% CI 22.5-29.1). The FOLFOXIRI arm was associated with higher G3-4 toxicity in form of neurotoxicity (5.2% vs.0%), neutropenia (50 % vs. 20.5%), febrile neutropenia (8.8% vs. 6.3%), vomiting (4.4% vs.3.2%), stomatitis (8.8% vs. 4.3%) and diarrhea (18.8% vs. 10.6%) [23].

This trial was conducted to compare the toxicity and efficacy of a combination of the three active agents capecitabine, oxaliplatin and irinotecan (using modified schedule of capecitabine of 7 days every 2 weeks and modified dose of irinotecan 165mg/m^2) combined with bevacizumab against the standard CAPEOX (capecitabine and oxaliplatin) plus bevacizumab.

Patients and Methods

This phase II randomized study that was carried out in Saudi German Hospital in KSA. Sixty five patients were enrolled between February 2013 and June 2015. Enrollment criteria included diagnosis of metastatic colon adenocarcinoma. All patients had unresectable either primary or metastatic lesions or both with at least one measurable distant metastatic visceral lesion. All patients should have ECOG performance status score of <2. All patients should have adequate organ function. The laboratory assessment for organ function should be normal at the start of treatment as follows: WBCs ›¯4000/ml, absolute neutrophil count ›¯1500/ml, PLT: ›¯100,000/ml, HB ›¯1 0gm/dl. All patients should have normal hepatic and renal function tests. Serum bilirubin was < Upper Limit of Normal (ULN), SGOT, SGPT, Alkaline Phosphatase (ALP) < 1.5 times ULN and serum creatinine < ULN. Left Ventricular Ejection Fraction (LVEF) ›¯50% was required. Each patient signed full informed consent. Approval was taken from ethical committee. Exclusion criteria included brain metastases, previous chemotherapy and significant co-morbid disease such as organ failure, marked neuropathy or ischemic heart disease with history of myocardial infarction in last one year.

Treatment:

Group A (33) patients received up to 12 cycles of BEV-CAPEOXIRI cycles at 14 days intervals. BEV-CAPEOXIRI regimen consisted of bevacizumab at a dose of 5mg/kg Intravenous Infusion (IVI) on day 1 (the first infusion was delivered over 90min, the second infusion over 1h, and subsequent infusions over 30min), capecitabine 850mg/m^2 twice orally daily within 30 minutes from meals and 12 hours interval from day 1 to day 7, oxaliplatin 85mg/m^2 IVI over 2 hours and irinotecan 165mg/m^2 IVI over 1 hour IVI. Loperamide 2mg oral q2hr and atropine 0.25mg subcutaneous injection were given to treat cholinergic symptoms.

Group B (32) patients received up to 12 cycles of BEV-CAPEOX at 21 days intervals. BEV-CAPEOX regimen consisted of bevacizumab at a dose of 7.5mg/kg IVI on day 1 (the first infusion was delivered over 90min, the second infusion over 1h, and subsequent infusions over 30min), capeciatbine 1000mg/m^2 twice orally daily within 30 minutes from meals and 12 hours interval from day 1 to day 14 and oxaliplatin 130mg/m^2 IVI over 2 hours day 1.

After a maximum of 12 cycles, oxaliplatin was stopped in both groups and irinotecan in group A. Patients continued on same scheduled chemotherapy doses of capecitabine and bevacizumab assigned for each group. Treatment was discontinued if disease progression, unacceptable toxicity or patient consent withdrawal.

Dose modifications:

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC; version 3.0) [24]. No dose reduction was allowed for bevacizumab. Treatment was continued at the same dose (without reduction or interruption) on occurrence of G1 toxicities. On first incidence of any G2 non hematological toxicity, treatment was delayed till recovery to G0-1 with no dose reductions. Treatment was to be resumed at 75% and 50% of original dose on second and third appearance of same G2 toxicity, respectively while to be discontinued on its fourth appearance. For G3 toxicity, dose was delayed till recovery to G0-1 toxicity then treatment was to be resumed at 75% and 50% of original dose on first and second occurrence of same toxicity, respectively while to be discontinued on its third appearance. In case of G4 neutropenic or thrombocytopenic toxicity, treatment was to be resumed at 75% of the original dose after recovery to G0-1and discontinued if repeated after dose reduction. Anemia was corrected with transfusions, with no dose reduction.

Initial assessment:

All eligible patients had a complete medical history and physical examination. Laboratory investigations included complete blood cell count (CBC) with differential count, serum bilirubin, AST, ALT, ALP, blood urea, serum creatinine and Carcino-Embryonic Antigen (CEA). Computerized tomography CT of abdomen and pelvis was done. Other imaging as Bone scan, CT chest or CT brain was done if clinically indicated.

Assessment of response:

Tumor response was assessed using computed tomography scans comparing baseline scans at study entry with that done every three cycles till progression. Reassessment was also done whenever progression was clinically warranted. If clinical complete response would had been occurred assessment was to be done every 3 months till relapse. Clinical response was defined based on standard RECIST (Response Evaluation Criteria in Solid Tumors) [25] as follows: Complete Response (CR) was defined as the complete disappearance of all disease lesions; Partial Response (PR) as a >30% reduction in the sum of the longest diameters of all measurable lesions; Stable Disease (SD) as a <30% reduction or a <20% increase in the sum of the longest diameters of all measurable lesions; and Progressive Disease (PD) was defined as >20% increase in the area(s) of original measurable lesion or the appearance of a new lesion [25]. Both CR and PR should be confirmed after 4 weeks.

Statistical methods:

The primary endpoint of the trial was the tumor overall response rate while the secondary end points including Progression Free Survival (PFS), Overall Survival (OS) and toxicity. The data were analyzed using the Statistical Product and Service Solutions SPSS 15.0 for Windows software. The Kaplan-Meier method was applied to estimate overall and progression-free survival outcomes [26]. The log-rank statistical test was used for univariate analysis of both PFS and OS in relation to the following factors: Treatment regimen, gender, ECOG performance status score, site of primary tumor (right versus left colon), resection status of primary tumor (resected versus not resected), presence of other sites of metastases other than liver, presence of peritoneal metastases and serum CEA level [27]. Descriptive statistics and the Kruskal-Wallis statistic test were utilized to compare patient criteria [28]. The Chi-square test and Fisher's exact test were used for comparative analysis between the two groups. A (p) value of less than 0.05 was considered statistically significant. Progression Free Survival (PFS) was measured starting from time of enrollment to first event of progression or last follow-up if no progression had happened. Overall Survival (OS) was estimated starting from time of enrollment to death from any cause or last follow-up.

Results

Patient characteristics:

Patient characteristics are summarized in (Table 1). A total of Sixty five patients (33 in BEV-CAPEOXIRI group and 32 in BEV-CAPEOX group) were enrolled between February 2013 and March 2015. No significant difference between the two groups except that BEV-CAPEOXIRI group had relatively more patients with peritoneal metastases than BEV-CAPEOX group (21% vs. 9%, respectively, p=0.19).

Treatment exposure and toxicity:

A total of 392 cycles (98% of planned cycles) were given in the BEV-CAPEOXIRI group versus 376 cycles in the BEV-CAPEOX group (97% of planned cycles). Two patients in BEV-CAPEOXIRI

group stopped treatment because of G4 diarrhea after 10 cycles and 3 patients in CAPEOX group stopped oxaliplatin because of G3 neurotoxicity (two patients after 9 and one after 10 cycles). Main causes of 1-2 weeks delay were G3-4 Neutropenia and diarrhea in BEV-CAPEOXIRI group versus G2 neurotoxicity and G2 palmar plantar erythrodysaesthesia in BEV-CAPEOX group. No dose reduction was allowed for bevacizumab. All patients received maintenance treatment except 2 patients in BEV-CAPEOXIRI and one patient in BEV-CAPEOX. The delivered relative dose intensity in BEV-CAPEOXIRI group was 100% for bevacizumab, 97% for capecitabine, 94% for oxaliplatin and 91% for irinotecan versus 100% for bevacizumab, 86% for capecitabine and 84% for oxaliplatin. The planned and relative dose intensities are presented in (Table 2).

Table (1): Patient characteristics.

Characteristics	BEV-CAPEOXIRI	BEV-CAPEOX	*p*
Number of patients	33	32	
Median age, years (range)	52 (37,60)	53 (40,62)	0.87
Gender:			
Male	14 (42%)	15 (47%)	0.72
Female	19 (58%)	17 (53%)	
Performance status (ECOG):			
0	15 (45%)	16 (50%)	0.89
1	7 (21%)	7 (22%)	
2	11 (34%)	9 (28%)	
Site of primary tumor:			
Right colon	18 (55%)	14 (44%)	0.38
Left colon	15 (45%)	18 (56%)	
Primary tumor resection:			
Resected	15 (45%)	14 (44%)	0.89
Unresected	18 (55%)	18 (56%)	
Site of metastases:			
Liver ± others*	33 (100%)	32 (100%)	0.35
Liver alone	18 (55%)	21 (66%)	
Liver + others	15 (45%)	11 (34%)	
Peritoneal + liver ± others	7 (21%)	3 (9%)	0.19
KRAS status:			
Mutated	24 (73%)	21 (66%)	0.75
Non-mutated	5 (15%)	5 (16%)	
Unknown	4 (12%)	6 (19%)	
Initial serum (CEA) level:			
≤5ng/ml	11 (33%)	8 (25%)	0.46
>5ng/ml	22 (67%)	24 (75%)	

*: Others include lung and bone.

Table (2): Planned and relative dose intensity in both treatment groups.

Medication / Dose intensity	BEV-CAPEOXIRI Planned (mg/m^2/week)	BEV-CAPEOXIRI Relative	BEV-CAPEOX Planned (mg/m^2/week)	BEV-CAPEOX Relative
Bevacizumab	2.73	100%	2.73	100%
Capecitabine	6490.9	97%	10181.8	89%
Oxaliplatin	46.36	94%	47.27	87%
Irinotican	90	91%	0	0

Adverse effects were mild to moderate (Table 3). The majority of side effects were in form of G1-2 toxicity. Diarrhea G3-4 occurred in 6 patients (18%) of BEV-CAPEOXIRI group versus 1 patient (3%) in BEV-CAPEOX group, p=0.04. Neutopenia G3-4 and febrile neutropenia occurred only in BEV-CAPEOXIRI group in 4 patients (12%) and 3 patients (9%), respectively, p=0.01 for neutropenia and p=0.02 for febrile neutropenia. G3 neurotoxicity occurred in 3 patients (9%) of BEV-CAPEOX group vs. 1 patient (3%) in BEV-CAPEOXIRI group, p= 0.01. Palmar plantar erythrodysaesthesia (hand and foot syndrome) G2 occurred in 21% versus 38% in BEV-CAPEOXIRI and BEV-CAPEOX group, respectively, p=0.04.

Table (3): Treatment related toxicity.

Toxicity	BEV-CAPEOXIRI (No.=33 patients) 1-2 No. (%)	BEV-CAPEOXIRI (No.=33 patients) 3-4 No. (%)	BEV-CAPEOX (No.=32 patients) 1-2 No. (%)	BEV-CAPEOX (No.=32 patients) 3-4 No. (%)	*p*
• Neutropenia	18 (55%)	4 (12)	11 (34)	0	0.01
• Neutropenic fever		3 (9)		0	0.02
• Anemia	6 (18)	1 (3)	2 (6)	0	0.04
• Thrombocytopenia	8 (24)	0	3 (9)	0	0.09
• Nausea	21 (64)	2 (6)	14 (44)	0	0.15
• Vomiting	5 (15)	2 (6)	4 (13)	0	0.28
• Diarrhea	12 (36)	6 (18)	7 (22)	1 (3)	0.04
• Stomatitis	11 (33)	2 (6)	3 (9)	1 (3)	0.03
• Lethargy	10 (30)	2 (6)	3 (9)	1 (3)	0.02
• Neurotoxicity	6 (18)	1 (3)	13 (41)	3 (9)	0.01
• Palmar-plantar erythrodsaesthesia	7 (21)	0	12 (38)	0	0.04
• Hypertension	2 (6)	0	3 (9)	0	0.56
• Proteinuria	2 (6)	0	1 (3)	0	0.45

Efficacy results:

Clinical response rates:

Clinical complete CR was not recorded. Twenty seven patients (82%) had clinical partial response (PR) in BEV-CAPEOXIRI group (A) versus 22 (69%) in BEV-CABEOX group (B), p=0.4 (Table 4). Three patients had stable disease in each group. Three (9%) versus 7 (22%) patients had progressive disease in group A versus B, respectively.

Table (4): Treatment response.

Response	BEV-CAPEOXIRI (33 patients)	BEV-CAPEOX (32 patients)	*p*
Complete (CR)	0	0	0.4
Partial (PR)	27 (82%)	22 (69%)	
Stable (SD)	3 (9%)	3 (9%)	
Progressive (PD)	3 (9%)	7 (22%)	

Survival analysis:

The cutoff date for this analysis was April 2018. After a median follow-up of 24 months (range, 10 to 31). Median Progression Free Survival (PFS)

in BEV-CAPEOXIRI was 15 months (95% Confidence Interval [CI]; 14, 16) versus 12 months in BEV-CAPEOX group (95% CI; 11, 13), p=0.01 Fig. (1).

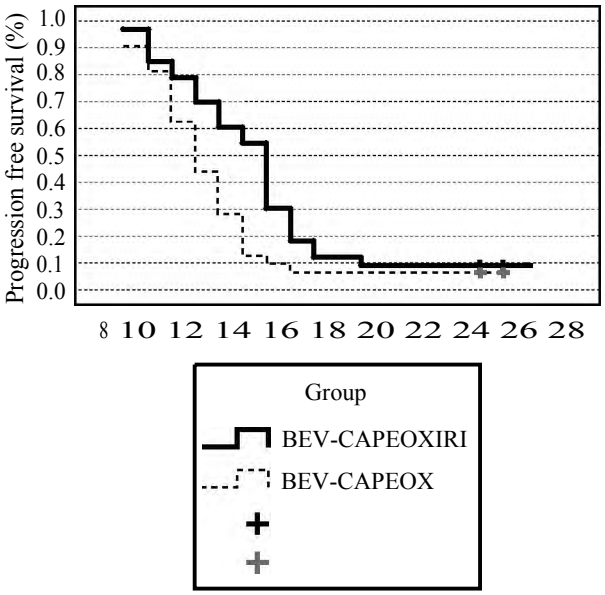

Fig. (1): Progression free survival in both treatment groups in months.

Seven patients (21%) remained alive in BEV-CAPEOXIRI (group A) versus 6 patients (19%) in BEV-CAPEOX (group B). Median OS in group A was 26 months (95% CI; 25, 27) versus 24 months in group B (95% CI; 23, 24), p=0.02 Fig. (2).

Table (5) shows that on univariate analysis, the prognostic factors associated with significantly longer PSF and OS were Type of treatment (BEV-CAPEOXIRI) and performance status (ECOG score ≤ 1) while those with shorter PFS and OS were presence of peritoneal metastases and involvement of liver plus other sites with metastases.

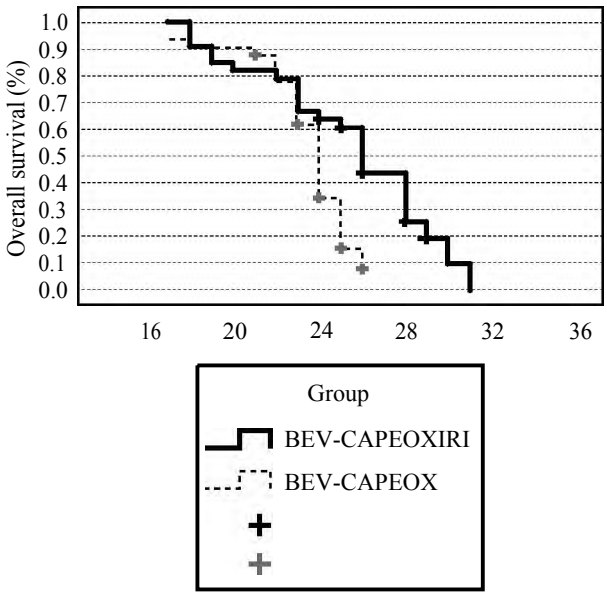

Fig. (2): Overall survival of both treatment groups in months.

Table (5): Univariate analysis of prognostic factors in relation to progression free survival (DFS) and Overall Survival (OS) rates.

Prognostic factor	Median PFS months ± SD (CI)	p log-rank	Median OS months ± SD (CI)	p log-rank
Gender:				
Female	12±0.7 (CI; 11, 13)	0.11	24±0.7 (CI; 23, 25)	0.54
Male	14±0.6 (CI; 13, 15)		25±0.9 (CI; 23, 27)	
ECOG performance score:				
0-1	14±0.4 (CI; 13, 15)	0.01	25±0.6 (CI; 24, 26)	0.02
2	10±0.3 (CI; 9, 11)		21±1.0 (CI; 19, 23)	
Colon primary site:				
Rt. colon	12±0.1 (CI; 10, 14)	0.48	24±0.7 (CI; 22, 25)	0.28
Lt. colon	13±0.6 (CI; 12, 14)		25±0.8 (CI; 23, 27)	
Primary colon tumor resected:				
Yes	15±0.5 (CI; 14, 16)	0.24	24±0.9 (CI; 22, 26)	0.09
No	14±0.5 (CI; 13, 15)		25±0.8 (CI; 23, 26)	
Liver and other sites metastases:				
Yes	11±0.6 (CI; 9, 12)	0.03	22±0.4 (CI; 21, 23)	0.04
No	14±0.5 (CI; 12, 15)		26±0.8 (CI; 24, 28)	
Peritoneal metastases:				
Yes	10±0.3 (CI; 9, 10)	0.01	18±0.4 (CI; 17, 19)	0.01
No	14±0.5 (CI; 13, 15)		25±0.5 (CI; 23, 26)	
CEA level in serum:				
≤5ng/ml	12±0.2 (CI; 11, 14)	0.25	23±0.8 CI; 22, 24)	0.12
>5ng/ml	13±0.8 (CI; 12, 15)		24±0.6 (CI; 23, 26)	
Treatment regimen:				
A*	15±0.5 (CI; 14, 16)	0.01	26±0.5 (CI; 25, 27)	0.02
B**	12±0.3 (CI; 11, 13)		24±0.4 (CI; 23, 24)	

*: BEV-CAPEOXIRI. **: BEV-CAPEOX.

Discussion

This study compared the efficacy and toxicity of the triple active chemotherapy medications: Beside bevacizumab regimen (BEV-CAPEOXIRI) consisting of a modified biweekly schedule of capecitabine and oxaliplatin plus iriontecan against the standard regimen of capecitabine, Oxaliplatin plus bevacizumab (BEV-CAPEOX). BEV-CAPEOXIRI had more favorable efficacy. Treatment in both groups was tolerable with no toxicity related death. The incidence of grade 3-4 neutropenia and diarrhea were higher in BEV- CAPEOX-IRI than BEV CAPEOX (12% vs. 0% and 18% vs. 3%, respectively). Neurotoxicity G1-2 and G3 were higher in BEV-CAPEOX than BEV-CAPEOX (41% and 9% vs. 18 and 3%, respectively). BEV-CAPEOX arm had also higher palmar plantar erythrodysaesthesia G1-2 (38% vs. 21%).

These results are similar to Bajetta et al., [29] and better than reported by Vasile et al., [30]. Bajetta et al., studied a biweekly schedule of capecitabine (Day 2-6) plus oxaliplatin and irinotecan (COI) combination that was associated with G3-4 diarrhea in 24% of the patients [29]. Vasile et al., reported that the major concern with the GONO- XELOXIRI regimen was the gastrointestinal toxicity, in particular, grade 3/4 diarrhea found in 30% of patients [30].

Sato et al., reported similar response rates and relatively higher incidence of G3-4 diarrhea [31]. Adverse effects associated with BEV-CAPEOX were similar to that recorded by Cassidy et al., [32] and Petrelli et al., [33]. Ducreux et al., reported that capecitabine plus oxaliplatin (XELOX) had grade 3/4 thrombocytopenia 12%, diarrhea 14%, neutropenia 5% without febrile neutropenia and neuropathy G3 in1 1% [34].

Bevacizumab related adverse effects were tolerable and manageable in both groups in form of G1-2 hypertension and proteinuria similar to that reported by Ducreux et al., [35]. No serious adverse effects as thromboembolic events or perforation were recorded.

Median PFS was significantly higher in BEV-CAPEOXIRI: 15 months (95% CI; 14, 16) versus 12 months in BEV-CAPEOX group (95% CI; 11, 13), p=0.01. Median OS was also significantly higher in BEV-CAPEOXIRI group (26 months) versus 24 months in BEV-CAPEOX (group B), p= 0.02.

XELOXIRI plus-Bevacizumab reported by Yuzhuo et al., achieved median PFS and OS of 10.8 months (95% CI, 8.9-12.8) and 23.7 months (95% CI, 18.1-31.6), respectively [36]. Zarate et al., reported that combination of capecitabine, oxaliplatin, irinotecan produced a median PFS and OS of 12 (95% CI; 10.6-13.4) and 27 months (95% CI; 17.2-36.8), respectively [37]. Bajetta et al., (COI) regimen achieved median PFS and OS 8.5 and 23.5 months, respectively [29]. Similar treatment outcome were reported by Fornaro et al., [38] and Mazard et al., [39] who treated their patients with capecitabine, oxaliplatin and irinotecan combination.

Capecitabine plus oxaliplatin (XELOX) achieved median progression-free survival was 8.8 months and median OS was 19.9 months, respectively [34].

Our study figures are higher than that reported in NO16966 study with XELOX and FOLFOX4, median OS was 19.0 and 18.9 months, respectively Saltz et al., [40].

Similar results to XELOX in our study were reported by Rothenberg et al., [41]. Cassidy et al., reported the NO16966 study, a median OS was 19.8 months was achieved with XELOX-bevacizumab [32]. Vasile et al., combination of irinotecan, oxaliplatin and capecitabine (XELOXIRI) achieved an overall response rate of 67% (95% CI 51.4-82%). After a median follow-up of 17.7 months, the median PFS and OS were 10.1 and 17.9 months, respectively [30].

Our results agree with that of Maroun et al., who studied a combination of irinotecan, capecitabine and oxaliplatin. They reported 67% objective response rate, 11 months median PFS and 25 months median OS [42].

On univariate analysis, peritoneal metastases were associated with shortest median OS and median PFS which similar to results of others [43-45]. Worthwhile noting that BEV-CAPEOXIRI group in our study had relatively more patients with peritoneal metastases in comparison to BEV-CAPEOX group (21% vs. 9%, respectively, p= 0.19). Other factors that were associated with poor results: Poor performance status ECOG score2, having hepatic and other distant metastases as lung and bone which agree with that reported by cetin et al., [46].

Treatment in both arms of this study was continued with maintenance capecitabine and bevacizumab which is reported to be of positive effect on treatment outcome as studied by Koopman et al., [47].

For future study: Larger randomized trials are needed to study this biweekly BEV-CAPEOXIRI regimen and compare it also with the intravenous regimen (bevacizumab + FOLFOXIRI) with consideration to assess quality of life.

Conclusion:

BEV-CAPEOXIRI had a more favorable treatment outcome (response rate, median PFS and OS) with lesser neurotoxicity & palmar plantar erythrodysaesthesia but higher manageable diarrhea and leucopenia in comparison to BEV-CAPEOX for patients with metastatic colon cancer. Larger randomized study is needed to confirm these results.

References

1- FERLAY J., SHIN H.R., BRAY F., et al.: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int. J. Cancer, 127: 2893-917, 2008.

2- SIEGEL R., NAISHADHAM D. and JEMAL A.: Cancer statistics, 2012. CA Cancer J. Clin., 62: 10-29, 2012.

3- JEMAL A., SIEGEL R., XU J. and WARD E.: Cancer statistics, 2010. CA Cancer J. Clin., 60: 277-300, 2010.

4- BEKAII-SAAB T. and WU C.: Seeing the forest through the trees: A systematic review of the safety and efficacy of combination chemotherapies used in the treatment of metastatic colorectal cancer. Crit. Rev. Oncol. Hematol., 91: 9-34, 2014.

5- VENDERBOSCH S., DOORNEBAL J., TEERENSTRA S., et al.: Outcome of first line systemic treatment in elderly compared to younger patients with metastatic colorectal cancer: A retrospective analysis of the CAIRO and CAIRO2 studies of the Dutch Colorectal Cancer Group (DCCG). Acta. Oncol., 51: 831-9, 2012.

6- De ROOCK W., De VRIENDT V., NORMANNO N., et al.: KRAS, BRAF, PIK3CA, and PTEN mutations: Implications for targeted therapies in metastatic colorectal cancer. Lancet Oncol., 12: 594-603, 2011.

7- MARTINELLI E., TROIANI T., MORGILLO F., et al.: Emerging VEGF-receptor inhibitors for colorectal cancer. Expert Opin. Emerg. Drugs, 18: 25-37, 2013.

8- VAN CUSTEM E., CERVANTES A., ADAM R., et al.: ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann. Oncol., 27: 1386-422, 2016.

9- CASSIDY J., TABERNERO J., TWELVES C., et al.: XELOX (capecitabine plus oxaliplatin): Active firstline therapy for patients with metastatic colorectal cancer. J. Clin. Oncol., 22: 2084-91, 2004.

10- MARTINEZ-BALIBREA E., ABAD A., ARANDA E., et al.: On behalf of the Spanish Group for the Treatment of Digestive Tumours (TTD) group: Pharmacogenetic approach for capecitabine or 5-fluorouracil selection to be combined with oxaliplatin as first-line chemotherapy in advanced colorectal cancer. Eur. J. Cancer, 44: 1229-37, 2008.

11- DIAZ-RUBIO E., GOMEZ-ESPANA A., MASSUTI B., et al.: First-line XELOX plus bevacizumab followed by XELOX plus bevacizumab or single-agent bevacizumab as maintenance therapy in patients with metastatic colorectal cancer: The phase III MACRO TTD study. Oncologist, 17: 15-25, 2012.

12- ROTHENBERG M.L., NAVARRO M., BUTTS C., et al.: Phase III trial of capecitabine + oxaliplatin (XELOX) vs. 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin (FOLFOX4) as 2nd line treatment for patients with metastatoc colorectal cancer (MCRC) (Abstract). J. Clin. Oncol., 25: 171s, 2007.

13- HALLER D.G., CASSIDY J., CLARKE S., et al.: Tolerability of fluoropyrimidines appears to differ by region (abstract). J. Clin. Oncol., 24: 149s, 2006.

14- HALLER D.G., CASSIDY J., CLARK S.J., et al.: Potential regional differences for the tolerability profiles of fluoropyrimidines. J. Clin. Oncol., 26: 2118, 2008.

15- CASSIDY J., CLARKE S., DÍAZ-RUBIO E., et al.: Randomized phase III Study of capecitabineplus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first line therapy for metastatic colorectal cancer. J. Clin. Oncol., 26: Page 2006, 2008.

16- PORSCHEN R., ARKENAU H.T., KUBICKA S., et al.: Colorectal Study Group Phase III study of capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: A final report of the AIO Colorectal Study Group. J. Clin. Oncol., 25: 4217-23, 2007.

17- DIAZ-RUBIO E., TABERNERO J., GOMEZ-ESPANA A., et al.: Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: Final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J. Clin. Oncol., 25: 4224-30, 2007.

18- DUCREUX M., BENNOUNA J., HEBBAR M., et al.: Efficacy and safety findings from a randomized 101 phase III study of capecitabine and oxaliplatin vs infusion 5-FU/LV + O (FOLFOX-6) for metastatic colorectal cancer (MCRC) (abstract). J. Clin. Oncol., 25: 170s, 2007.

19- FUCHS C.S., MARSHALL J., MITCHELL E., et al.: Randomized, Controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in firs-line treatment of metastatic colorectal cancer: Results from the BICC-C Study. J. Clin. Oncol., 25: 4779, 2007.

20- GUO Y., SHI M., SHEN X., et al.: Capecitabine plus irinotecan versus 5- FU/leucovorin plus irinotecan in the treatment of colorectal cancer: A meta-analysis. Clin. Colorectal. Cancer, 13: 110, 2014.

21- HURWITZ H., FEHRENBACHER L., NOVOTNY W., et al.: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N. Engl. J. Med., 350: 2335, 2004.

22- HURWITZ H.I., TEBBUTT N.C., KABBINAVAR F., et al.: Efficacy and safety of bevacizumab in metastatic colorectal cancer: Pooled analysis from seven ramdomized controlled trials. Oncologist, 18: 1004, 2013.

23- CREMOLINI C., LOUPAKIS F., ANTONIOTTI C., et al.: FOLFOXIRI plus Bevacizumab versus FOLFIRI plus Bevacuzumab as first line treatment of patients with metastatic colorectal cancer: Updated overall survival and molecular subgroup analyses of open label, phase 3

TRIBE Study. The Lancet oncology, 16 (13): 1306-15, 2015.

24- Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Bethesda, MD: Cancer Therapy Evaluation Program, 2006 (http://ctep.cancer.gov/ rotocolDevelopment/electronic_applications/ docs/ctcaev3.pdf) 2006.

25- THERASSE P., ARBUCK S.G., EISENHAUER E.A., et al.: New guidelines to evaluate the response to treatment in solid tumors. J. Natl. Cancer Inst., 92: 205-16, 2000.

26- KAPLAN E.L. and MEIER P.: Non-parametric estimation from incomplete observations. J. Am. Stat. Assoc., 53: 457-81, 1958.

27- PETO R. and PIEK M.C.: Conservation of the approximation (O-E) 2/E in the log-rank test for survival data on tumor incidence rate. Biometrics., 29: 579-84, 1973.

28- SPURRIER J.D.: On the null distribution of the Kruskal-Wallis statistic. Journal of Nonparametric Statistics, 15 (6): 685-91, 2003.

29- BAJETTA E., CELIO L., FERRARIO E., et al.: Capecitabine plus oxaliplatin and irinotecan regimen every other week: A phase I/II study in first-line treatment of metastatic colorectal cancer. Ann. Oncol., 18: 1810-6, 2007.

30- VASILE E., MASI G., FORNARO L., et al.: A multicenter phase II study of the combination of oxaliplatin, irinotecan and capecitabine in the first-line treatment of metastatic colorectal cancer. Br. J. Cancer, 100: 1720-4, 2009.

31- SATO Y., OHNUMA H., HIRAKAWA M., et al.: A dose-escalation study of oxaliplatin/capecitabine/irinotecan (XELOXIRI) and bevacizumab as a first-line therapy for patients with metastatic colorectal cancer. Cancer Chemother Pharmacol., 75: 587-94, 2015.

32- CASSIDY J., CLARKE S., DIAZ-RUBIO E., et al.: XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. Br. J. Cancer, Jun. 28; 105 (1): 58-64, 2011.

33- PETRELLI F., COINU A., GHILARDI M., et al.: Efficacy of oxaliplatin-based chemotherapy + bevacizumab as first-line treatment for advanced colorectal cancer: A systematic review and pooled analysis of published trials. Am. J. Clin. Oncol., Apr., 38 (2): 227-33, 2015.

34- DUCREUX M., BENNOUNA J., HEBBAR M., et al.: GI Group of the French Anti-Cancer Centers. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int. J. Cancer, Feb. 1; 128 (3): 682-90, 2011.

35- DUCREUX M., ADENIS A., PIGNON J.P., et al.: Efficacy and safety of bevacizumab-based combination regimens in patients with previously untreated metastatic colorectal cancer: Final results from a randomised phase II study of bevacizumab plus 5-fluorouracil, leucovorin plus irinotecan versus bevacizumab plus capecitabine plus irinotecan (FNCLCC ACCORD 13/0503 study). Eur. J. Cancer, 49: 1236-45, 2013.

36- YUZHUO CHENG and WEILIANG SONG: Efficacy of FOLFOXIRI versus XELOXIRI plus bevacizumab in the treatment of metastatic colorectal cancer. Int. J. Clin. Exp. Med., 8 (10): 18713-20, 2015.

37- ZARATE R., RODRÍGUEZ J., BANDRES E., et al.: Oxaliplatin, irinotecan and capecitabine as first-line therapy in metastatic colorectal cancer (mCRC): A dose-finding study and pharmacogenomic analysis. Br. J. Cancer, Mar. 16; 102 (6): 987-94, 2010.

38- FORNARO L., MASI G., BURSI S., et al.: A dose finding and pharmacokinetic study of capecitabine in combination with oxaliplatin and irinotecan in metastatic colorectal cancer. Cancer Chemother. Pharmacol., 63: 965-9, 2009.

39- MAZARD T., YCHOU M., et al.: Feasibility of biweekly combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in patients with metastatic solid tumors: Results of a two-step Phase I trial: XELIRI and XELIRINOX. Cancer Chemother. Pharmacol., 69 (3): 807-14, 2012.

40- SALTZ L.B., CLARKE S., DIAZ-RUBIO E., et al.: Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: A randomized phase III study. J. Clin. Oncol., 26: 2013-9, 2008.

41- ROTHENBERG M.L., COX J.V., BUTTS C., et al.: Capecitabine plus oxaliplatin (XELOX) vs 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX-4) as second-line therapy in metastatic colorectal cancer: A randomized phase III noninferiority study. Ann. Oncol., 19: 1720-6, 2008.

42- MAROUN J., MARGINEAN H., JONKER D., et al.: A phase I Study of Irinotecan, Capecitabine(XELODA) and Oxaliplatin in patients With Advanced Colorectal Cancer. Clinical Colorectal Cancer, 17, 2: e257-68, June 2018.

43- LEMMENS V.E., KLAVER Y.L., VERWAAL V.J., et al.: Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: A population-based study. Int. J. Cancer, 128: 2717-25, 2011.

44- SEGELMAN J., GRANATH F., HOLM T., et al.: Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br. J. Surg., 99: 699-705, 2012.

45- FRANKO J., SHI Q., GOLDMAN C.D., et al.: Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: Apooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J. Clin. Oncol., 30: 263-7, 2012.

46- CETIN B., KAPLAN M.A., BERK V., et al.: Prognostic factors for overall survival in patients with metastatic colorectal carcinoma treated with vascular endothelial growth factor-targeting agents. Asian Pac. J. Cancer Prev., 13 : 1059-63 , 10379, 2012.

47- KOOPMAN M., SIMKENS L., MAY A., et al.: Final results and subgroup analyses of the phase 3 CAIRO3 study: Maintenance treatment with capecitabine and bevacizumab versus observation after induction treatment with chemotherapy and bevacizumab in metastatic colorectal cancer (mCRC). J. Clin. Oncol., 32: Suppl 3: LBA388. Abstract, 2014.

دراسة عشوائية من المرحلة الثانية بين بروتوكول من بيفاسى ذوماب وكابسيتابين وآوكساليبلاتين وايرينوتيكان كل آسبوعين وبروتوكول من بيفاسى ذوماب وكابسيتابين وآوكساليبلاتين كل ثلاثة آسابيع فى علاج سرطان القولون المنتشر

الخلفية العلمية: من المعروف آن البروتوكول من بيفاسى وكابيسيتابين وآوكساليبلاتين ذو فاعلية فى علاج سرطان القولون المنتشر وكذلك الآيرونيتيكان.

الهدف من الدراسة: آجريت هذه الدراسة لمقارنة السمية والفاعلية للبروتوكول المذكور الذى يؤخذ كل ثلاثة آسابيع ضد بروتوكول مكون من نفس الآدوية معدلة الجرعات مضافا إليها الآيرينوتيكان يؤخذ كل آسبوعين.

المرضى وطرق البحث: تمت الدراسة على خمسة وستين مريضا بسرطان القولون المنتشر لم يسبق علاجهم كيميائيا حيث تم تقسيمهم عشوائيا إلى مجموعتين: المجموعةالآولى ضمت ثلاثة وثلاثون (٣٣ مريضا) آخذوا بيفاسى ذوماب وكابيسيتابين وآوكساليبلاتين وايرينوتيكان كل آسبوعين والمجموعة الثانية ضمت (٣٢ مريضا) آخذوا بيفاسى ذوماب وكابيسيتابين وآوكساليبلاتين كل ثلاثة آسابيع.

النتائج: كانت نسبة حدوث الدرجة ٣-٤ من نقص الخلايا البيضاء ونقص الخلايا المتعادلة ذى الحمى والإسهال آعلى فى المجموعة الآولى وهى على الترتيب (١٢٪ ضد ٠٪ و٩٪ ضد ٠٪ و١٨ ضد ٣٪) بينما كانت نسبة حدوث السمية العصبية الطرفية من الدرجة ١-٢ والدرجة ٣ آعلى فى المجموعة الثانية (٩ & ٤١٪ ضد ١٨٪ & ٣ فى الآولى) وكذلك كانت المجموعة الثانية آعلى فى معدل حدوث إحمرار باطن اليدين والقدمين المتغير الحس من الدرجة ١-٢ (٣٨٪ ضد ٢١٪) بالترتيب. وبمقارنة المجموعة الآولى ضد الثانية كان معدل الإستجابة جزئيا آعلى فى الآولى ٨٢٪ ضد ٦٩٪ ومعدل تزايد المرض آقل فى الآولى ٩٪ ضد ٢٢٪ وثبات المرض ٩٪ فى كل المجموعتين. وكان متوسط الحياة العام ومتوسط الحياة دون تزايد المرض آعلى بآهمية إحصائيا فى المجموعة الآولى ٢٦ شهرا ضد ٢٤ شهرا و١٥ شهرا ضد ١٢ شهرا على الترتيب.

الخاتمة: البروتوكول المكون من بيفاسى ذوماب وكابيسيتابين وآوكساليبلاتين مع الآيرينوتيكان كل آسبوعين آعلى فاعلية فى معدل الإستجابة ومتوسط الحياة العام والحياة دون تفاقم المرض وآقل فى السمية العصبية وإحمرار باطن اليدين والقدمين ذى الحس المتغير بينما هو آعلى إحداثا للإسهال ونقص الخلايا المتعادلة مع إمكانية علاجهما بالمقارنة للبروتوكول المكون من بيفاسى ذوماب وكابيسيتابين وآوكساليبلاتين كل ثلاثة آسابيع.