ORIGINAL ARTICLE



UDC: 616-006::616.348/.351-006-085 DOI: 10.2298/VSP150513173J

## Efficacy and safety of bevacizumab in combination with irinotecan and capecitabine in first-line treatment of metastatic colorectal cancer

Efikasnost i sigurnost bevacizumaba u kombinaciji sa irinotekanom i kapecitabinom u prvoj liniji lečenja metastatskog kolorektalnog karcinoma

Saša Jungić\*, Biljana Tubić<sup>†</sup>, Radoslav Gajanin<sup>‡</sup>, Zdenka Gojković\*, Ivanka Rakita\*

\*Clinic of Oncology, <sup>‡</sup>Department of Pathology, University Clinical Center Banjaluka, Banjaluka, Bosnia and Herzegovina; <sup>†</sup>Agency for Medicines and Medical Devices of Bosnia and Herzegovina, Banjaluka, Bosnia and Herzegovina

#### Abstract

**Background/Aim**. The efficacy and safety of bevacizumab (BEV) in combination with capecitabin and irinotecan in first-line therapy for patients with metastatic colorectal cancer (mCRC) were studied. In order to improve safety and efficacy of chemotherapy, as well as to reduce adverse reactions to a minimum, doses of active agents applied were changed in relation to previously employed schedules. **Methods**. Patients with histologically documented mCRC with no previously received chemotherapy or with received adjuvant or neoadjuvant chemotherapy, which ended 6 months before capecitabin treatment (1000 mg/m<sup>2</sup> *per os* from the 2nd to 8th day of each cycle), irinotecan (175 mg/m<sup>2</sup> *iv* every 2 weeks), plus bevacizumab (5 mg/kg *iv* every 2 weeks) were observed. **Results**. This prospective study included 35 patients of both sexes. The overall response rate (ORR) of 28.6%, partial response (PR) of 28.6%, progressive disease (PD) of 28.6% and stable disease (SD)

#### Apstrakt

Uvod/Cilj. U radu je ispitivana efikasnost i bezbednost terapije prve linije protokolom XIA (kapecitabin/irinotekan/bevacizumab) kod bolesnika sa metastatskim kolorektalnim karcinomom (mCRC). U cilju povećanja podnošljivosti i efikasnosti hemoterapije, kao i da bi se neželjeni efekti sveli na minimum, doze aktivnih agenasa su unekoliko promenjene u odnosu na ranije primenjivane šeme. Metode. Ispitanici sa mCRC koji nisu prethodno primali hemioterapiju, ili su primali adjuvantnu ili neoadjuvantnu hemioterapiju završenu šest meseci pre početka lečenja lečeni su prema sledećoj terapijskoj shemi: kapecitabin (1000 mg/m2 per os od 2. do 8. dana svakog ciklusa), irinotekan (175 mg/m² iv svake 2 sedmice) u kombinaciji sa bevacizumabom (5 mg/kg iv svake 2 sedmice). Rezultati. Ovo prospektivno ispitivanje vršeno je na ukupno 35 ispitanika oba pola. Ukupni odgovor [overall response rate (ORR)] bio je postignut kod 28,6%, parcijalan odgovor (PR) kod 28,6% bolesnika, do progresije bolesti (PD) došlo je kod

of 42.8% were found. The progression-free survival (PFS) of the analyzed patients was 11.3 (95% CL: 9.1–12.9) months while overall survival (OS) of the included patients was 25.2 (95% CL: 17.4–28.4) months and 117 adverse effects were recorded in 24 patients. Alopecia, nausea and vomiting, hemorrhage, hand-foot syndrome, diarrhea, abdominal pain, proteinuria, and hypertension (51.4%, 37.1%, 37.1%, 25.7%, 22.8%, 20.0%, 20.0% and 17.1%, respectively) were most frequently observed adverse effects. **Conclusion**. The results of this clinical trial support and recommend the use of bevacizumab plus capecitabin and irinotecan in the doses and schedule applied throughout this study as the first-line treatment of mCRC patients.

#### Key words:

# colorectal neoplasms; neoplasm metastasis; antineoplastic combined chemotherapy protocols; drug toxicity.

28,6% i stabilna bolest (SD) kod 42,8%. Preživljavanje bez progresije bolesti (PFS) iznosilo je 11,3 meseca (interval pouzdanosti – 95% CL: 9,1 – 12,9 meseci). Ukupno preživljavanje [overall survival (OS)] ispitanika bilo je 25,2 meseca (95% CL: 17,4 – 28,4 meseca). Kod 24 ispitanika zapaženo je 117 neželjenih reakcija. Najčešće neželjene reakcije bile su alopecija, mučnina i povraćanje, hemoragija, sindrom šaka-stopalo, dijareja, abdominalni bol, proteinurija i hipertenzija (51,4%, 37,1%, 37,1%, 25,7%, 22,8%, 20,0%, 20,0% i 17,1%, respektivno). **Zaključak**. Rezultati ispitivanja podržavaju i opravdavaju dodatak bevacizumaba hemioterapijskoj kombinaciji kapecitabin/irinotekan u prvoj liniji lečenja bolesnika sa mCRC, kao i primenjene doze prema korišćenoj shemi.

#### Ključne reči:

kolorektalne neoplazme; neoplazme, metastaze; lečenje kombinovanjem antineoplastika, protokoli; lekovi, toksičnost.

**Correspondence to:** Biljana Tubić, Department for Medicines for Human Use, Agency for Medicines and Medical Devices of Bosnia and Herzegovina, Veljka Mladjenovica bb, 78 000 Banjaluka, Bosnia and Herzegovina. Phone: +387 51 450 304, Fax: +387 51 45 0301, E-mail: <u>b.tubic@almbih.gov.ba</u>

#### Introduction

Colorectal cancer (CRC) represents the third most frequently diagnosed malignancy and the second main cause of fatal outcome of cancer patients in the world<sup>1</sup>.

The introduction of novel drugs in the systemic treatment of mCRC during the last two decades leads to increased median survival in clinical trials from 6-9 months to over 2 years<sup>2</sup>.

Irinotecan in combination with 5-fluorouracil (5-FU)based chemotherapy and bevacizumab (BEV) represent an established option in the treatment of mCRC<sup>2</sup>. Continuous infusion of 5-FU in addition to irinotecan (FOLFIRI) has been found to be more effective and tolerable than bolus of 5-FU<sup>3</sup>. However, this regimen requires hospitalization or the placement of central venous line. In contrast, the irinotecan-capecitabine combination (XELIRI) appears to be more convenient<sup>3</sup>. In the Bolus, Infusional, or Copecitabine with Camptosar-Celecoxil (BICC-C) randomized trial, XELIRI in comparison with FOLFIRI, was associated with higher rates of severely expressed undesirable side effects such as nausea, vomiting, diarrhea, dehydration, handfoot syndrome and as a consequence, treatment discontinuation. Also, progression-free survival (PFS) was shorter in patients treated with XELIRI, when only patients who had completed the treatment, were compared <sup>3</sup>.

In the beginning of the 21st century, the European Medicines Agency (EMA) approved bevacizumab (BEV), a recombinant human monoclonal antibody, targeting vascular endothelial growth factor (VEGF), for first-line therapy of patients with advanced CRC, based on the data from the phase III American Venous Forum (AVF)2107g trial <sup>4</sup>. This trial demonstrated an increased response rate (RR), with a prolonged median duration of survival, as well as a longer median PFS.

After its introduction, fluoropyrimidine-based chemotherapy has been the mainstay for CRC treatment. Capecitabine represents an oral fluoropyrimidine of similar efficacy to 5-fluorouracil/leucovorin (5-FU/LV) as first-line treatment of advanced or mCRC <sup>5, 6</sup>. However, it is advantageous in comparison with 5-FU/LV because of its comfortable oral administration and satisfactory safety profile <sup>7</sup>.

The combination of BEV and capecitabin was shown to act synergistically, with a prolonged tumor inhibition period than achieved with either agent alone <sup>1</sup>. Similarly, in several phase I and II trials it has been observed that capecitabine and irinotecan (XELIRI) can be equally effective and safely combined in the most convenient alternative XELIRI regimen in individuals with advanced CRC, with no pharmacokinetic interactions <sup>1,8,9</sup>.

Based on the results of a previous clinical study on mCRC patients, it was clear that a biweekly combination of irinotecan and capecitabine expressed a synergistic effect, with an acceptable response rate (RR) of 32% and a satisfying tolerability as first-line therapy, together with an important time to progression of 9 months and an overall survival (OS) of 19.2 months in this advanced setting <sup>1</sup>.

Based on the aforementioned facts, it was to be expected that the combination of BEV with this biweekly XELIRI treatment scheme would be at least as effective as the standard FOLFIRI regimen with a more satisfactory safety profile. The data on efficiency of BEV administered together with capecitabine and irinotecan in patients with mCRC are relatively sparse in the available literature. This prompted us to evaluate the efficacy and safety of capecitabine, irinotecan, bevacizumab (XIA) regimen, as first-line treatment of mCRC patients.

The primary objective of this work was to determine the PFS, safety and tolerability to the XIA regimen. Secondary objectives included overall response rate (ORR) and OS.

#### Methods

A total of 35 patients suffering from initially unresectable chemotherapy-naïve mCRC were included in the present study. The examined group was formed according to the following criteria: adults of both sexes, age range 27–69 years; Eastern Cooperative Oncology Group (ECOG) performance status  $\leq 2$ ; adequate bone marrow function (neutrophil count  $\geq 1.5 \times 10^9$ /L, platelet count  $\geq 100 \times 10^9$ /L, hemoglobin  $\geq 9$  g/dL); serum creatinine < 1.25 mg/dL; alanine aminotransferase or aspartate aminotransferase or alkaline phosphatase < 3 times the upper limit of normal and keratin  $\leq 1.5$  times the upper limit of normal. Previous adjuvant or neoadjuvant chemotherapies had been completed at least 6 months before enrolment in the study.

The patients were treated with BEV 5 mg/kg on day 1 as 90/60/30-min intravenous infusion, followed by irinotecan 175 mg/m<sup>2</sup> as a 120-min intravenous infusion on day 1 and capecitabine 1,000 mg/m<sup>2</sup> orally twice daily from the day 2 to the day 8 (XIA schedule). All the patients were receiving serotonin 5-HT<sub>3</sub> (chemoreceptor trigger zone) inhibitors for nausea and vomiting prophylaxis. They were subjected to this treatment schedule (XIA) every 2 weeks in continuo until 12 cycles were completed except in the cases of disease progression, patient refusal, unacceptable toxicity or death. Appropriate dose interruptions/reductions were implemented in the case of specific toxicities, depending on their nature and intensity. The next course of treatment began only when the neutrophil count reached >  $1.5 \times 10^{9}$ /L, the platelet count >  $100 \times 10^{9}$ /L, and while any other treatment-related toxicity was lower than or equal to that found at grade 1.

A screening assessment including medical history, physical examination and chest radiography was conducted within 2 weeks before the onset of the treatment. Within 7 days before starting the treatment, further assessments included vital signs, ECOG performance status and laboratory tests (hematology, blood chemistry including liver and renal function tests and urine analyses). The assessment of the response was based on investigator-reported measurements according to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)<sup>10</sup>.

The study was performed in accordance with the Declaration of Helsinki. In addition, the approval of the responsible Ethics Committee was provided.

#### Statistical methods

Toxicity and safety were assessed in terms of toxicity and evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), Version 3.0.

Descriptive data were reported as proportion and medians. PFS was defined as the period from the date of the first dose of treatment applied to the first observation of disease progression or death by any cause. The OS was calculated as the period from the date of the first cycle of treatment until death of any cause or until the date of the last follow-up at which data point was censored. Survival analysis (PFS and OS) was estimated by the Kaplan–Meier method <sup>11</sup>.

#### Results

A total of 35 consecutive mCRC patients were treated by XIA regimen. The first patient was included in the study on October 19, 2005 and the latest one on November 30, 2010. From all 35 patients, seven were alive in December, 2012 and three of them had a second-look operation. One of the patients of this group of three was first included in the study in October, 2006 and one in July, 2010.

Baseline characteristics for the evaluable patients are

summarized in Table 1. Median age was 50.8 (range 27–69) years. All the 35 patients had an ECOG performance status of < 2 at baseline, half of them had multiple sites of metastases mostly located in the liver. A total of 22 out of 35 patients had initial mCRC.

#### Toxicity and dose administration

Out of 35 patients 33 received 12 cycles of XIA (94.3%) and a total of 396 XIA cycles were administered. Overall, 11.4% (n = 4) of patients required reduction of the dose by 25%. Treatment interruption because of BEV-related toxicity was required in a single patient. Treatment delays due to toxicity caused by capecitabine, irinotecan and BEV were required in two patients. The treatment was rather well tolerated and most of the reported undesirable side effects were mildly expressed according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE grade 1 or 2).

The main hematology and non-hematology toxicities are summarized in Table 2.

Table 1

	Table 1				
Baseline patient characteristics					
Characteristics of the patients $(n = 35)$	Values				
Median age (years), mean (range)	50.85 (27-69)				
Sex, n (%)					
male	16 (45.7)				
female	19 (54.3)				
Grade of disease in the initial diagnosis, (II/III/IV), n	25/5/0				
State of disease in the initial diagnosis (2/3/4), n	6/7/20				
Localization (colon/rectum/colorectal), n	19/10/6 (54.3/28.6/17.1)				
Previous therapy, n (%)					
chemotherapy	10 (28.6)				
radiotherapy	0 (0)				
Chemotherapy (Adjuvant therapy), n (%)					
5FU/FA	7 (20)				
FUP	2 (6)				
capecitabine	1 (3)				
Surgery of primary tumor, n (%)	34 (97)				
Number of metastatic sites, n (%)					
1	17 (48)				
2	14 (40)				
3	2 (6)				
4	2 (6)				

5FU/FA - 5 fluorouracil/folinic acid; FUP - follow-up protocol.

#### Table 2

Most frequent treatment-related adverse events <i>per</i> patient							
Adverse event	Grade 1/2		Grade 3/4		Total		
	n	%	n	%	n	%	
Alopecia	18	51.4	_	_	18	51.4	
Vomiting and Nausea	13	37.1			13	37.1	
Hemorrhage	13	37.1	_	_	13	37.1	
Leukopenia	9	25.7	1	2.8	10	28.6	
Hand-foot syndrome	9	25.7		_	9	25.7	
Diarrhea	8	22.8	_	_	8	22.8	
Abdominal pain	7	20.0			7	20.0	
Proteinuria	7	20.0			7	20.0	
Hypertension	6	17.1	—		6	17.1	
Fever	4	11.4			4	11.4	
Mucositis	3	8.6	—	—	3	8.6	
Local pain	2	5.7			2	5.7	
Thrombocytopenia	2	5.7	—	—	2	5.7	
Hyperbilirubinemia	2	5.7	_	_	2	5.7	
Numbness of extremities	2	5.7			2	5.7	
Anorexia	2	5.7	_	—	2	5.7	
Enteritis	_	_	1	2.8	1	2.8	
Ileus	_		1	2.8	1	2.8	

Jungić S, et al. Vojnosanit Pregl 2017; 74(3): 249-255.

Vol. 74, No. 3

The most common grade 1/2 toxicities were: alopecia, vomiting and nausea, hemorrhage, leukopenia, hand-foot syndrome, diarrhea, abdominal pain, proteinuria and hypertension (51.4%, 37.1%, 37.1%, 28.6%, 25.7%, 22.8%, 20.0%, 20.0% and 17.1%, respectively).

The adverse reactions, toxicity grade 3/4 were: leukopenia, enteritis and ileus (2.8% each).

No treatment-related deaths were reported.

During the present study, a total of 117 adverse reactions were observed and in 24 out of 35 patients involved in the trial, the number of adverse events grade 1 was 94 (80%), those of grade 2 was 18 (16%) and those of grade 3 was 5 (4%). No adverse reactions of grade 4 were recorded.

A total of 11 (31%) patients did not express the signs of adverse reactions, while 7 (20%) patients suffered one of adverse reactions. Two adverse reactions were observed in 4 (11%) patients and only a single patient suffered from twelve of these reactions.

#### Efficacy and survival

As shown in Table 1 XIA regimen led to a partial response in 10 out of 35 (28.6%) patients. Fifteen (42.8%) patients had a stable form of the disease and 10 (28.6%) had a progressive disease (Table 3).

	Table 3				
Response of the patients to the treatment applied					
Response to the treatment	Patients, n (%)				
Complete response	0 (0)				
Partial response	10 (28.6)				
Stable disease	15 (42.8)				
Progressive disease	10 (28.6)				
R0 resection	3 (8.6)				

R0 - nula resection (microscopically margin-negative resection).

PFS was 11.3 months (95% confidence interval CI: 9.1–12.9) (Figure 1). OS was 25.2 months (95% CI: 17.4–28.4 months) (Figure 2), and ORR was 28.6%.

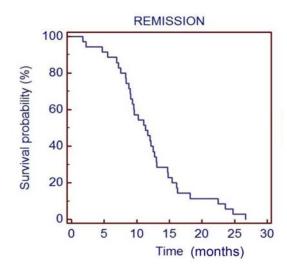


Fig. 1 – Kaplan-Meier survival estimates of progression-free survival.

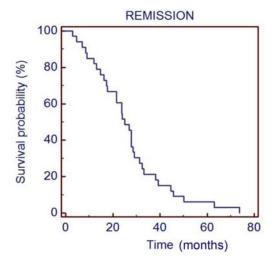


Fig. 2 - Kaplan-Meier survival estimates of overall survival.

#### Discussion

Based on the results obtained in 2 phase III randomized controlled trials (RCTs) several authors have demonstrated the improved survival of advanced CRC patients upon BEV addition to standard 5-FU-based chemotherapy regimens in combination with irinotecan (IFL) and oxaliplatin (FOLFOX4)<sup>4, 12, 13</sup>. It was also shown that PFS was significantly improved in the bevacizumab-containing arms of all three studies <sup>12, 14</sup>. Both survival and response rates were similarly improved in randomized phase II trials comparing 5-FU/FA combined with BEV with 5-FU/FA alone in advanced CRC patients <sup>12, 15, 16</sup>. Survival benefit was observed after BEV had been added to 5-FU regimens given by bolus injection (IFL) and by continuous infusion (FOLFOX). BEV in combination with 5-FU-based chemotherapy has been shown to be effective in both first- and second-line treatments of advanced CRC<sup>12</sup>.

BEV in combination with any fluoropyrimidine-based chemotherapy was more effective than any fluoropyrimidinebased chemotherapy alone. This conclusion was confirmed by two extensive registry trials in first-line mCRC — the Bevacizumab Regimens Investigation of Treatment Effects and Safety (BriTE) trial in the United States <sup>12</sup> and the First BEV Expanded Access Trial (BEAT) performed in Europe and Canada<sup>12, 17</sup>. The above-mentioned trials were designed to evaluate safety events of BEV applied in combination with a variety of chemotherapy regimens in a broad community-based population of mCRC patients. These observational data strongly suggest that BEV in combination with a variety of fluoropyrimidine-based chemotherapy regimens was safe, with efficacy similar to that seen in prospective randomized clinical trials. However, achievement of OS and PFS benefits in BEV-supplemented chemotherapy led to a significant toxicity increase. Commonly observed undesirable side effects in clinical trials with BEV included bleeding, thrombosis, hypertension and proteinuria. Luckily, the hypertension could be managed using oral antihypertensive drugs, but it required frequent blood pressure monitoring <sup>12</sup>.

Reported and ongoing phase III trials have excluded patients with cerebral metastases, advanced atherosclerotic disease, or proteinuria. Therefore, these conditions should be considered contraindicative to BEV application. Throughout the above clinical trials, rare cases of BEV-associated gastrointestinal perforation and poor wound healing were seen <sup>11, 17–19</sup>. At present, there is no evidence to support the use of BEV as monotherapy in advanced CRC <sup>12, 13</sup>. Thus, BEV should not be taken as an alternative in the third-line setting of systemic treatment of advanced CRC.

Regarding colon cancer, the results of Wagner et al.<sup>20</sup> were supported by other meta-analyses evaluating the addition of BEV to chemotherapy in the metastatic setting <sup>12, 20–22</sup>. These should be interpreted in the light of the disease specific survival of different malignancies. Therefore, 3 months of survival benefit in metastatic colon cancer when the expected OS is over 20 months differs from a 3 month-benefit in a patient with metastatic lung or pancreatic cancer in which the median survival is under 12 months <sup>19, 23</sup>. The role of PFS as a surrogate for overall survival has been extensively debated in metastatic cancer <sup>19</sup>.

To date, there has been limited data on the XELIRI plus BEV regimen<sup>1</sup>. Available data presenting preliminary results from a study using BEV with irinotecan plus capecitabine showed that this combination had a promising clinical activity. Garcia-Alfonso et al.<sup>1</sup> reported an ORR of 40%, with an overall disease control rate of 86% and a year progression-free rate of 49%. At The Annual Meeting of the American Society of Clinical Oncology (ASCO) held in 2009, these authors presented preliminary results of the phase II, non-comparative, randomized FNCLCC ACCORD 13/0503 trial, in which a total of 145 patients, age range 18-72 years, were randomized to receive either BEV plus XELIRI (irinotecan 200 mg/m<sup>2</sup> on day 1, capecitabine 1000  $mg/m^2$  twice daily on days 1 – 14 plus BEV 7.5 mg/kg on day 1, every 3 weeks) or BEV plus FOLFIRI (irinotecan 180  $mg/m^2$  on day 1 plus 5-FU 400  $mg/m^2$  plus leucovorin 400 mg/m2 on day 1 followed by 5-FU 2400 mg/m<sup>2</sup> as a 46hour-infusion plus BEV 5 mg/kg on day 1, every 2 weeks). Preliminary results from the first 6-month follow-up showed an ORR of 58% (95% CI: 47-70%) in the BEV plus XELIRI arm similar to 58% (95% CI: 53-65%) in the BEV plus FOLFIRI arm. The most common grade 3/4 advese reactions reported in the XELIRI and FOLFIRI groups were neutropenia (17% vs 26%), diarrhea (12% vs 5%) and cardiovascular events (13% vs 11%). The authors concluded that XELIRI and FOLFIRI plus BEV expressed similar efficiency in the treatment of mCRC patients with manageable toxicity.

Garcia-Alonso et al.<sup>1</sup> in a single-institutional study applied the combination of biweekly XELIRI plus BEV for previously untreated mCRC patients and observed beneficial effects of the treatment with an ORR of 67.4%, a median PFS of 12.3 months and a median OS of 23.7 months. The overall disease control rate was 93.5%.

The results of our single-institutional study with the XIA regimen applied to previously untreated mCRC patients also revealed a meaningful clinical activity, with an ORR of 28.6%, a median PFS of 11.3 months, and a median OS of

25.2 months. Analysis of efficacy results demonstrated a higher percentage of stable disease (SD) in our test protocol, in relation to the partial response (PR), as compared to a comparative study. This difference could be ascribed to a lower grade of main adverse events in our study. Also, it should be noted that during the study protocol, there was no complete response (CR), but 7 patients (20.0%) were alive and 3 of them operated on. In general, this drug combination was relatively well tolerated, with most of adverse events grades being 1/2. Interestingly, the overall safety profile of this combination differs from those achieved with the XELIRI regimen<sup>1, 24</sup>. In the BICC-C trial, the XELIRI arm was associated with a significantly higher incidence of grade 3/4 diarrhea (48%), neutropenia (32%) and dehydration  $(19\%)^{3}$ . In the 40015 clinical trial conducted by the EORTC group, XELIRI was associated with increased mortality, as well as an almost 40% incidence of grade 3/4 diarrhea<sup>1, 24</sup>. In these two clinical trials, the increased toxicity clearly impacted the clinical activity of the XELIRI regimen in a negative manner. However, it is worth mentioning that the doses of XELIRI applied in these studies were higher comparing to those used in our XELIRI plus BEV combination described here.

Compared to the recent findings of the Ducreux's trial employed by García-Alfonso et al.<sup>1</sup> who investigated the combination of XELIRI and FOLFIRI along with BEV, the clinical activity of the data reported in the present study in terms of ORR was similar to that reported for the FNCLCC ACCORD 13/0503 trial. However, better toxicity profile achieved in our study could be interpreted to be the result of the lower dose of chemotherapeutic agents in XELIRI plus BEV regimen described here.

Comparative analyses of the efficacy results of the XIA protocol and those obtained in the corresponding studies of others demonstrated a higher percent of SD in relation to a partial regression. Besides, the percent of low grade adverse reactions (grades 1 and 2) found throughout the present study could be connected to a high percent of SD. Doses of capecitabine and irinotecan in XIA protocol are the same in comparison with other regimens with capecitabine, irinotecan and bevacizumab, but in our XIA schedule doses of irinotecan and bevacizumab are differently deployed, and because of that we got better results of the tolerance of therapy.

The patients had the same response as patients in similar protocols, so efficiency is comparable to existing protocols (equal to them). But toxicity is lower, that is, the safety is improved, because the dose of irinotecan is better tolerated if distributed in the manner that the irinotecan is administered for 14 days, but not on the day 21 (as is customary).

The XIA protocol examined here expressed a better tolerance but equal PFS and OS suggesting a beneficial effect achieved after dividing daily dose of the drugs applied into several lower doses. In this way toxicity decrease of the therapy employed can be achieved while PFS and OS remain unchanged. At the same time lower percent of total and partial regression of the disease was observed strongly suggesting the application of this newly created protocol for therapeutic maintenance during continual and intermittent treatments. This could also result from lower grade of adverse reactions comparing to those reported in comparative studies of other authors. In addition, it should be noticed that CR was absent when XIA protocol was applied, but six patients were operated on and three of them were still alive.

The distribution and percent of adverse reactions were oscillating both in the present study and in the reports of the others. The reasons for these variations could be ascribed to the differences in evaluation procedures, but also to the differences in time schedules of hormonal therapy (HT) + BEV application (every two or three weeks). Also, the differences

- 1. García-Alfonso P, Muñoz-Martin AJ, Alvarez-Suarez S, Jerez-Gilarranz Y, Riesco-Martinez M, Khosravi P, et al. Bevacizumab in combination with biweekly capecitabine and irinotecan, as first-line treatment for patients with metastatic colorectal cancer. Br J Cancer 2010; 103(10): 1524-8.
- 2. Fuchs CS, Marshall J, Barrueco J. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: Updated results from the BICC-C study. J Clin Oncol 2008; 26(4): 689-90.
- 3. Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, 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(30): 4779-86.
- 4. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004; 350(23): 2335-42.
- 5. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. J Clin Oncol 2001; 19(8): 2282-92.
- 6. Van Cutsem E, Hoff PM, Harper P, Bukowski RM, Cunningham D, Dufour P, et al. Oral capecitabine vs intravenous 5-fluorouracil and leucovorin: Integrated efficacy data and novel analyses from two large, randomised, phase III trials. Br J Cancer 2004; 90(6): 1190-7.
- 7. Scheithauer W, Kornek GV, Raderer M, Schüll B, Schmid K, Kovats E, et al. Randomized multicenter phase II trial of two different schedules of capecitabine plus oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2003; 21(7): 1307-12.
- 8. Tewes M, Schleucher N, Achterrath W, Wilke HJ, Frings S, Seeber S, et al. Capecitabine and irinotecan as first-line chemotherapy in patients with metastatic colorectal cancer: Results of an extended phase I study. Ann Oncol 2003; 14(9): 1442-8.
- 9. Bajetta E, Di Bartolomeo M, Mariani L, Cassata A, Artale S, Frustaci S, et al. Randomized multicenter phase II trial of two different schedules of irinotecan combined to capecitabine as first line treatment in metastatic colorectal cancer. Cancer 2004; 100(2): 279-87.
- 10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). EJC 2009; 45(2): 228-47.

in bioavailability and equivalency of novel and generic drugs should be taken into account.

#### Conclusion

Based on the results obtained throughout the present study it can be concluded that the combination of BEV with the XELIRI regimen is feasible with manageable toxicity. Besides, it is associated with a promising efficacy in terms of PFS, ORR and OS in previously untreated mCRC patients.

### REFERENCES

- 11. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-81.
- 12. Welch S, Spithoff K, Rumble RB, Maroun J. Gastrointestinal Cancer Disease Site Group. Bevacizumab combined with chemotherapy for patients with advanced colorectal cancer: A systematic review. Ann Oncol 2010; 21(6): 1152-62.
- 13. Giantonio BJ, Catalano PJ, Meropol NJ, O'dnyer PJ, Mitchell EP, Alberts SR, et al. 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(12): 1539-44.
- 14. Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, 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 2008; 26(12): 2013-9.
- 15. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, 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(1): 60-5.
- 16. Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht RJ, et al.. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: Results of a randomized phase II trial. J Clin Oncol 2005; 23(16): 3697-705.
- 17. van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, Dibartolomeo M, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLIRI and fluoropyrimidines in metastatic colorectal cancer: The BEAT study. Ann Oncol 2009; 20(11): 1842-7.
- 18. Saif MW, Elfiky A, Salem RR. Gastrointestinal perforation due to bevacizumab in colorectal cancer. Ann Surg Oncol 2007; 14(6): 1860-9.
- 19. Amit L, Ben-Aharon I, Vidal L, Leibovici L, Stemmer S. The impact of Bevacizumab (Avastin) on survival in metastatic solid tumors: A meta-analysis and systematic review. PLoS ONE 2013; 8(1): e51780.
- 20. Wagner AD, Arnold D, Grothey AA, Haerting J, Unverzagt S. Anti-angiogenic therapies for metastatic colorectal cancer. Cochrane Database Syst Rev 2009; 8(3): CD005392.
- 21. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: A meta-analysis. Lancet Oncol 2007; 8(10): 898-911.
- 22. Loupakis F, Bria E, Vaccaro V, Cuppone F, Milella M, Carlini P, et al. Magnitude of benefit of the addition of bevacizumab to

first-line chemotherapy for metastatic colorectal cancer: Metaanalysis of randomized clinical trials. J Exp Clin Cancer Res 2010; 29(1): 58.

- Ocaña A, Amir E, Vera F, Eisenhauer EA, Tannock IF. Addition of Bevacizumab to Chemotherapy for Treatment of Solid Tumors: Similar Results but Different Conclusions. JCO 2011; 29(3): 254–6.
- 24. Köhne CH, De Greve J, Hartmann JT, Lang I, Vergauwe P, Becker K, et al. Irinotecan combined with infusional 5-fluorouracil/folinic

acid or capecitabine plus celecoxib or placebo in the first-line treatment of patients with metastatic colorectal cancer. EORTC study 40015. Ann Oncol 2008; 19(5): 920–6.

Received on May 13, 2015. Revised on November 27, 2015. Accepted on December 1, 2015. Online First July, 2016.