JBUON 2017; 22(5): 1131-1136
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Evaluation of safety of bevacizumab as second-line treatment of patients with metastatic colorectal cancer

Vladimir Todorovic, Nada Cicmil Saric, Jadranka Lakicevic, Milan Sorat
Oncology Clinic, Clinical Centre of Montenegro, Podgorica, Montenegro

Summary

Purpose: *Bevacizumab is a relatively new monoclonal antibody introduced in the treatment of metastatic colorectal cancer (CRC). Since varied efficiency and adverse events of this drug were reported, the purpose of this study was to assess the safety of bevacizumab as second-line treatment of patients with metastatic CRC.*

Methods: *This observational, non-interventional study involved 35 patients with metastatic CRC treated with bevacizumab. Patients were from the Oncology Clinic, Clinical Centre of Montenegro. Monitoring of patients was done according to the study protocol.*

Results: *The number of subjects with abnormal values of tumor marker CEA has decreased from 56.8% (enrollment visit) to 50% in the sixth visit ($p<0.01$). The number of subjects with abnormal values for tumor marker Ca19-9 ranged from initial 45% (enrollment visit) to 50% on the sixth visit ($p>0.05$). No significant differences in the average values of hematological and biochemical parameters and the average values of the CEA and Ca19-9 were noticed.*
In 26 (46.2%) patients, adverse events were recorded. Of 72 adverse events, 31 (43.05%) were related to bevacizumab. Regarding adverse events intensity, 68.1% were moderate. The most common adverse event was hypertension, which was recorded in 12 patients. There was no life-threatening adverse event connected with the drug use.

Conclusion: *Use of bevacizumab caused moderate adverse effects, none of which was life-threatening.*

Key words: *bevacizumab, metastatic colorectal cancer, patient safety*

Introduction

CRC is one of the most common malignancies worldwide. With more than 1.2 million newly diagnosed cases, it is the third most common cancer in men and the second most common in female population [1,2]. CRC is a leading cause of cancer-related death with almost 700,000 deaths per year [3,4]. At the time of diagnosis 15-25% of the patients have metastatic disease, whereas 40-50% of patients will develop metastasis during the course of the disease [4,5]. Chemotherapy is standard treatment in patients with metastatic CRC. Although the prognosis is poor, in the last few years with new medications (fluoropyrimidine, irinotecan, oxaliplatin) significant progress in the treatment of metastatic CRC was noticed, which resulted in significant improvement of treatment outcomes and prolongation of survival [6,7].

One of the new generation products used in the treatment of metastatic CRC is the humanized monoclonal antibody bevacizumab. This drug binds to vascular endothelial growth factor (VEGF), which induces the active growth of tumor blood vessels supplying the tumor with nutrients and oxygen. The binding of bevacizumab to VEGF disables the regular effect of VEGF, thus preventing tumor growth [7,8]. This applies in the first, the second and subsequent lines of treatment of patients with metastatic colorectal, breast, kidney and lung cancer [9]. While some studies indicate that bevacizumab prolongs disease free survival

Correspondence to: Vladimir Todorovic, MD, PhD. Oncology Clinic, Clinical Center of Montenegro Ljubljanska bb, Podgorica, Montenegro.
Tel: +38269388069, E-mail: vladimir.todorovic@kccg.me
Received: 23/05/2017; Accepted: 04/06/2017

[10-12], other studies point to the limits of its effectiveness and safety [13-15].

The purpose of this study was to assess the safety of bevacizumab as second-line treatment of patients with metastatic CRC.

Methods

This non-observational study was conducted between May 2009 and March 2014 at the Oncology Clinic, Clinical Centre of Montenegro. The study enrolled 35 patients with metastatic CRC.

Inclusion criteria

Inclusion criteria of the study were: signed informed consent, age above 18 years, ability to co-operate during the study, histologically or cytologically proven CRC, measurable or non-measurable disease according to RECIST criteria, life expectancy ≥3 months, ECOG performance status (PS) of 0-1, normal renal function (serum creatinine ≤1.25), proteinuria <2+, normal liver function (total bilirubin <1.5 , AST, ALT <2.5 for patients with no metastasis in the liver; AST, ALT <5 the upper limit of normal in patients with liver metastasis and dysfunction. Alkaline phosphatase (AP) <2.5 times the upper limit of normal, the corresponding hematological parameters (neutrophils ≥1.5 x 10^9/l, platelets ≥100 x 10^9/l, ≤1.5 INR, PTT ≤1.5 times the upper limit of normal for a period of 7 days before inclusion) and negative pregnancy test.

Exclusion criteria

Exclusion criteria were: clinically significant cardiovascular disease (stroke ≤6 months; heart attack ≤6 months; heart weakness NYHA grade II or more, serious cardiac arrhythmias), current or recent (within 10 days from the first doses of bevacizumab) use of oral or parenteral anticoagulants or thrombolytic agents in full treatment dose (prophylactic use of anticoagulants allowed), use of aspirin (325 mg/day) or other drugs that can cause gastrointestinal ulceration, participation in a clinical study in the previous 3 months, pregnancy or breastfeeding, surgical intervention 28 days before the start of the study, presence of thrombosis and hemorrhagic diseases, serious unhealed wound or ulcer or bone fracture, evidence of bleeding diathesis or coagulopathy, uncontrolled hypertension, CNS metastases, known hypersensitivity to bevacizumab or any auxiliary component, or to any type of chemotherapy, proof of any neural disease or metabolic dysfunction, established disease or condition contraindicated for the use of the study drug.

Bevacizumab was administered as intravenous 60-min infusion as second-line treatment of metastatic CRC after progression to the previously administered chemotherapy. Patients were receiving intravenous infusion every 2 to 3 weeks (10 mg/kg when given in 2 weeks, or 15 mg/kg when given in 3 weeks). Patients' visits were every 2 months as defined by the protocol and the last visit was 30 days after the last treatment. The evaluation of treatment response was done every 3 months and was based on the following parameters: physical examination, evaluation of hematological and serum biochemical parameters, protein analysis of urine, thoracic and abdominal CT and tumor markers.

Statistics

The Statistical Package for Social Sciences (SPSS v 20) was used for statistical analyses. For continuous variables, the number of subjects (n), mean±standard deviation, median and range were registered, whereas for qualitative variables, absolute and relative frequency distribution were recorded. For calculating the differences between more than two-time periods, repeat ANOVA test was used. For calculating differences between two periods the *post hoc* test was used. Categorical data were analyzed by chi square test. In all tests, a p value <0.05 was considered as statistically significant.

Results

Women represented 48.6%, and men 31.9% of the study population (Table 1). The average age of patients was 57.6 ± 9.5 years, ranging from 39 to 74 years. The largest number of patients was in the age group of 60 to 65 years (20.0%) (Table 1).

Data analysis found variations in the values of CEA and Ca 19-9. On the enrollment visit, Ca19-9 was measured in 35 patients with average value of 280.0 ± 502.2 U/ml, while the maximum recorded value was 2219/ml. On the sixth visit, this tumor marker was detectable in only two patients. The maximal value of this tumor marker registered during the study was 2364 U/ml (Table 2).

As for CEA, its average value was 245.0±444.9 ng/ml on the enrollment visit, and up to 17.3±12.9 ng/ml on sixth visit. Despite the absolute value, this drop was not statistically significant (p>0.05) owing to the small number of patients in the sixth visit (2 patients) with detectable CEA (Table 2). The maximal value of CEA registered during the investigation was 5035 ng/ml.

The differences between the average values of CEA and Ca 19-9 during the study were statistically nonsignificant (p>0.05).

The percentage of patients with abnormal values of CEA (>5ng/ml) was 91.4% on the en-

Table 1. Socio-demographics variables at the enrollment visit

	Total number of patients (35)	x^2, *p*
Gender, n (%)		>0.05
Male	17 (48.6)	
Female	18 (51.4)	
Age, years (mean±SD)	57.6±9.5	

SD: standard deviation

Table 2. Average values of CEA and Ca19-9

Visits	*Statistics*	*Ca19-9 (U/ml)*	*CEA (ng/ml)*
Visit 0: enrollment visit	n	*35*	*35*
	Mean±SD	280±502.22	245±444.89
	Min-Max	2-2219.0	2.5-1570.4
Visit 1	n	34	34
	Mean±SD	177.1±328.79	393±940.27
	Min-Max	3.8-1326	2.0-5053
Visit 2	n	25	25
	Mean±SD	362.8±736.33	184.6±353.90
	Min-Max	2-2364	1.1-1481.7
Visit 3	n	19	19
	Mean±SD	114.8±273.62	145.2±444.58
	Min-Max	2-1200	1.4-1970
Visit 4	n	12	12
	Mean±SD	36.4±39.77	49.9±78.13
	Min-Max	2-107.2	2-286.2
Visit 5	n	7	7
	Mean±SD	68.3±64.56	93.3±168.88
	Min-Max	2.5-162	1.8-471.5
Visit 6	n	2	2
	Mean±SD	24.4±15.98	17.3±20.71
	Min-Max[a]	13.1-35.7	2.6-31.9
	p[b]	p>0.05	p>0.05

[a]minimum-maximum;
[b]repeated measures ANOVA; SD: standard deviation; n: number of patients;
Note: All changes were not statistically significant (p>0.05)

rollment visit, and 50% on the sixth visit. These results should be interpreted with caution due to the small number of patients in the sixth visit (n=2). This decrease was statistically significant (p<0.01) (Figure 1). On the enrollment visit 45.7% of the patients had abnormal Ca19-9 (>37U/ml), while the percentage of patients with abnormal values on the sixth period was 50% (p>0.05) (Figure 1).

During 8 visits (enrollment visit, 6 control and final visit), the average values of hematological and biochemical parameters were followed. The average values of red and white blood cells counts varied during the 8 visits, but remained within normal range (p>0.05). The average value of neutrophils during the enrollment visits was higher than the reference values, and their decrease during 8 visits was not statistically significant (p>0.05). The average values of monocytes, eosinophils and basophils had a tendency to fall insignificantly during treatment (p>0.05). The average values of platelets and hemoglobin, and also the biochemical parameters (ALT,AST,AP,LDH,albumin,serum creatinine, glucose, Na, K) remained within normal range during the investigation.

A total number of 26 (46.2%) patients experienced 72 adverse events: 1 adverse effect in 8 patients (19.6%), 2 in 7 patients (16.6%), 3 in 4 patients (15.2%), 4 in 2 patients (7.5%), 5 in 3 (11.4%) patients, 6 in 1 patient, and 9 in 1 patient. In most patients (42.3%) the higher intensity of adverse events was moderate; in 13.9% the intensity was mild, in 12.5% was serious and in one patient (5.5%) the adverse effect was life-threatening. In more than half of the patients (54.2%) adverse events were not associated with the study drug. Of 72 adverse events, 9 were probably related, while 22 were possibly related with the drug. The number of adverse events associated with confirmed relationship with the study drug was 31 (Table 3). Of 72 adverse events, 39 had recovery as outcome, 26 had progression as an outcome, while 7 adverse events resulted in death.

Adverse events probably or possibly related with the study drug had mild or moderate intensity. Life-threatening adverse events were not related to the study drug.

Hypertension was registered in 12 patients, while in one patient loss of appetite, fever, angina pectoris with hypertension, dysuria, poor appetite and diarrhea were registered.

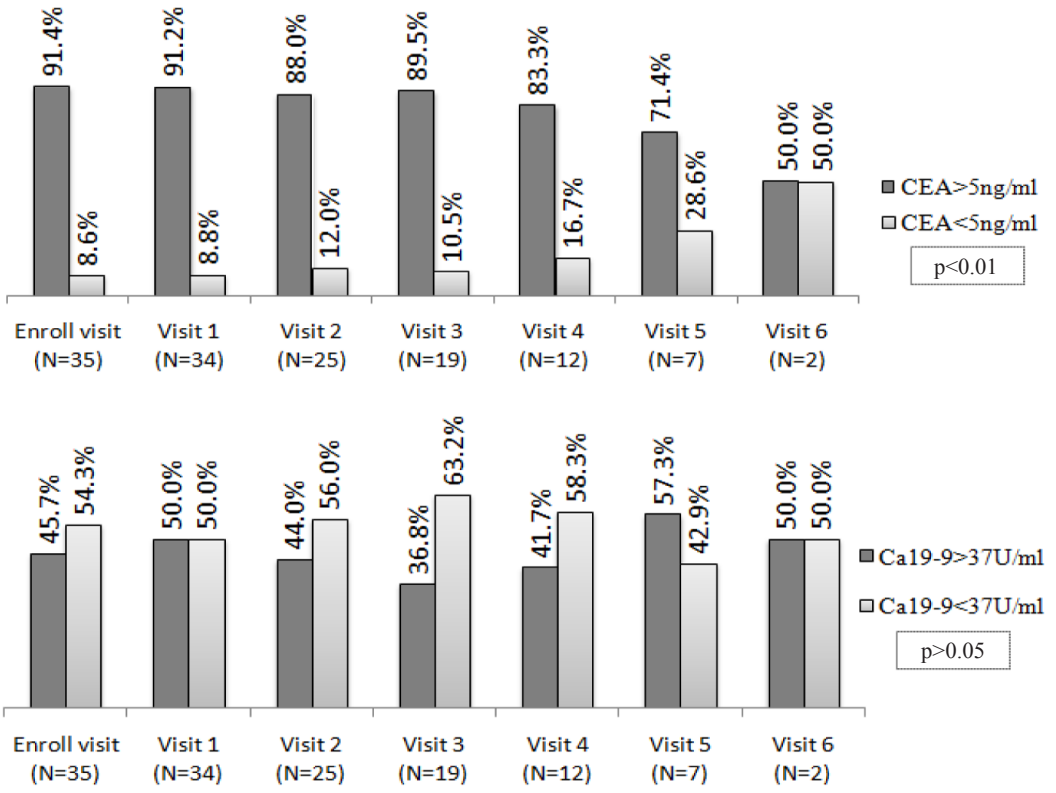

Figure 1. The number of patients with abnormal values of CEA and Ca19-9 during the study.

Table 3. Summary of adverse events during the study

Adverse events	*n/total patients (%)*	*n /total n events*
Any adverse event	26/35 (74.3)	72
Intensity of adverse event		
Mild		10/72 (13.9)
Moderate		49/72 (68.1)
Serious		9/72 (12.5)
Life-threatening		4/72 (5.5)
The relationship between drug and adverse events		
Probable		9/72 (12.5)
Possible		22/72 (30.6)
Unknown		2/72 (2.8)
Unrelated		39/72 (54.2)
Outcome of the undesired event		
Recovery		39/72 (54.2)
Up to date		26/72 (36.1)
Unknown		0/72 (0)
Death		7/72 (9.7)
Number of adverse events		
	8/26 (31.6)	1
	7/26 (26.7)	2
	4/26 (15.2)	3
	2/26 (7.5)	4
	3/26 (11.4)	5
	1/26 (3.8)	6
	1/26 (3.8)	9

n: number

Discussion

Our research was intended to investigate the safety of bevacizumab use in patients with metastatic CRC. For safety evaluation, serum biochemical and hematological parameters were registered and followed. Due to lack of available information in the literature about the correlation of hematological and biochemistry parameters, it was not possible to compare the values of the present study.

From the literature review, it is possible to conclude that the values of CEA with other clinically relevant parameters can be used for diagnosis of metastatic disease and for evaluation of therapeutic efficiency [16-19]. Besides CEA, other tumor markers like CA 19-9 and CA 242 can be used [20]. In our study, values of CEA and Ca19-9 varied. No statistically significant differences were found in their average values, possibly attributed to the small patient sample examined in the study, as well as the decreasing number of patients during the study. The study started with 35 patients enrolled and ended up with 19. Seven patients were excluded from the study for various reasons (refusing to continue treatment, adverse events, rejection, and no cooperation in accordance with the study protocol). Seven patients died. Treatment for one patient has been changed.

Petrioli et al. demonstrated that the increased values of CEA and Ca 19-9 may indicate progression of disease in patients who are using bevacizumab [21]. The results of Formica and co-workers study indicate that Ca19-9 values can be used as an effective indicator of bevacizumab efficacy, whereas for CEA this correlation was not demonstrated [22].

The results of our study showed that 74.3% of the examined patients reported a total of 72 adverse events during bevacizumab usage, of which 31 events were related to the study drug. Similar results were obtained in a Japanese study, in which 66% of the patients experienced adverse events related with the study drug [23]. The most frequently reported adverse event was hypertension related with bevacizumab, reported in 12 (34.28%) patients, which matches with the results of other studies in which the most common adverse event was hypertension [24-27].

In conclusion, bevacizumab seems to be a rather safe drug, since neither severe adverse effects nor death occurred in patients treated with it.

Conflict of interests

This study was sponsored by Hoffmann-La Roche Ltd Podgorica.

References

1. Wang Z, Liang L, Yu Y et al. Primary Tumor Resection Could Improve the Survival of Unresectable Metastatic Colorectal Cancer Patients Receiving Bevacizumab-Containing Chemotherapy. Cell Physiol Biochem 2016;39:1239-46.
2. Ohhara Y, Fukuda N, Takeuchi S et al. Role of targeted therapy in metastatic colorectal cancer. World J Gastrointest Oncol 2016;8:642-55.
3. González Alonso VN, Arroyo G, Martinez J et al. Predictive biomarkers candidates for patients with metastatic colorectal cancer treated with bevacizumab-containing regimen. Drug Metab Pers Ther 2016;31: 83-90.
4. Zhao L, Wang J, Lee H et al. Meta-analysis comparing maintenance strategies with continuous therapy and complete chemotherapy-free interval strategies in the treatment of metastatic colorectal cancer. Oncotarget 2016;7:33418-28.
5. Avallone, Piccirillo CM, Aloj L et al. A randomized phase 3 study on the optimization of the combination of bevacizumab with FOLFOX/OXXEL in the treatment of patients with metastatic colorectal cancer-OBELICS (Optimization of bevacizumab scheduling within Chemotherapy Scheme). BMC Cancer 2016;4:69.
6. Bronte G, Silvestris N, Castiglias M et al. New findings on primary and acquired resistance to anti-EGFR therapy in metastatic colorectal cancer: all roads lead to RAS? Oncotarget 2015;6:24780-96.
7. Cavic M, Krivokuca A, Boljevic et al. Pharmacogenetics in cancer therapy – 8 years of experience at the Institute for Oncology and Radiology of Serbia. JBUON 2016;21:1287-95.
8. Instructions for Patients - Summary of product characteristics, Medicines and Medical Devices Agency of Serbia, November, [cited 2016 November 16]. http://www.alims.gov.rs/ciril/files/lekovi/pil/6554-2010-12.pdf
9. Jain RK, Duda DG, Willett CG et al. Biomarkers of response and resistance to antiangiogenic therapy. Nat Rev Clin Oncol 2009;6:337-8.
10. Bennouna J, Sastre J, Arnold D et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomized phase 3 trial. Lancet Oncol 2013;14:29-37.
11. Masi G, Salvatore l. Bonnie L et al. Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized trial BEBYP. Ann Oncol 2015;26:723-30.
12. Bayoglu V, Yildiz I, Varol U et al. Comparison of first-line bevacizumab in combination with mFOLFOX6 or XELOX in metastatic colorectal cancer. JBUON 2015;20:460-7.
13. Emmanouilides C, Pegram M, Robinson R et al. Anti-VEGF antibody bevacizumab (Avastin) with 5FU/LV as third line treatment for colorectal cancer. Tech Coloproctol 2004;8:50-2.
14. Geva RL, Vecchione T, Piessevaux H et al. Bevacizumab plus chemotherapy as salvage treatment in chemorefractory patients with metastatic colorectal cancer. Onco Targets Ther 2013;6:53-8.
15. Kang BW, Kim TW, Lee JL et al. Bevacizumab plus FOLFIRI or FOLFOX as third-line or later treatment in patients with metastatic colorectal cancer after failure of 5-fluorouracil, irinotecan, and oxaliplatin: analysis and retrospective programmes. Med Oncol 2009;26:32-7.
16. Duffy M. Tumor Markers in Clinical Practice: A Review Focusing on Common Solid Cancers. Med Princ Pract 2013;22:4-11.
17. Abe S, Kawai K, Ishihara S et al. Prognostic impact of carcinoembryonic antigen and carbohydrate antigen 19-9 in stage IV colorectal cancer patients after R0 resection. J Surg Res 2016;205:384-92.
18. Park IJ, Choi GS, Lim KH et al. Serum carcinoembryonic antigen monitoring after curative resection for colorectal cancer: clinical significance of the preoperative level. Ann Surg Oncol 2009;16:3087-93.

19. Yakabe T, Nakafusa Y, Sumi K et al. Clinical significance of CEA and CA19-9 in postoperative follow-up of colorectal cancer. Ann Surg Oncol 2010;17:2349-56.
20. Sturgeon C, Duffy M, Stenman et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers. Clin Chem 2008;54:11-79.
21. Petrioli R, Licchetta A, Roviello G et al. CEA and CA19.9 as early predictors of progression in advanced/metastatic colorectal cancer patients receiving oxaliplatin-based chemotherapy and bevacizumab. Cancer Invest 2012;30:65-71.
22. Formica V, Massara MC, Portarena I et al. Role of CA19.9 in predicting bevacizumab efficacy for metastatic colorectal cancer patients. Cancer Biomark 2009;5:167-75.
23. Hatake K, Doi T, Uetake H, Takahashi Y, Ishihara Y, Shirao K. Bevacizumab safety in Japanese patients with colorectal cancer. Jpn J Clin Oncol 2016;46:234-40.
24. Cutsem E, Rivera F, Berry S et al. for the First BEAT investigators. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX VERSUS, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol 2009;20:1842-7.
25. Kozloff, M Yood, Berlin J et al. for the investigators of the BRiTE study. Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: observational cohort study the BRiTE. Oncologist 2009;14:862-70.
26. Hurwitz H, Saini V. Bevacizumab in the treatment of metastatic colorectal cancer: safety profiles and management of adverse events. Semin Oncol 2006;33:26-34.
27. Chen C, Sun P, Ye S et al. Hypertension as a predictive biomarker for efficacy of bevacizumab treatment in metastatic colorectal cancer: a meta-analysis. J BUON 2014;19:917-24.