Efficacy and safety of bevacizumab in combination with oxaliplatin, irinotecan and fluoropyrimidine-based therapy in advanced colorectal cancer

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SUMMARY

Background: *Bevacizumab is an anti-VEGF, humanized mAb that is the most advanced agent of its class in clinical development. Several studies have examined bevacizumab in combination with chemotherapy in the first- and second-line settings in patients with metastatic CRC. Despite of that, there is lack of information concerning the extent to which bevacizumab can be used to treat metastatic CRC. We still need more evidence related to efficacy and safety of bevacizumab in different settings, or sequential treatments. The aim of this study was to investigate efficacy and safety of bevacizumab added to different chemotherapy in patients with metastatic CRC.*

Methods: *This was a controlled, prospective, multicentre, cohort study. Thirty patients with advanced colorectal cancer were enrolled into this study. Bevacizumab was applied with oxaliplatin-, irinotecan-, 5FU- or capecitabine -based chemotherapy in the first-, second- or third-therapy lines. Totally 261 cycles were applied. The median number of applied cycles per patient was 8 (range 2-16).*

Results: *Objective tumor response (RR) was seen in 11 patients 37% (95%CI 19-69%) calculated on an intention-to-treat basis. The median duration of response was 12 months. Three of 11 patients (27%) with PR had secondary surgery. RR was seen in 9 of 16 patients (56%) who received bevacizumab in the first-line treatment and in 2 of 14 patients (14%) who received therapy in the second+ lines (p=0.02). Clinical benefit (PR+SD) was seen in 22 (74%) patients. 75% of patients achieved clinical benefit in the first-line and 74% in the second+ chemotherapy lines. The median time to progression (TTP) of the patients is was 9 + months (95%CI 7 - + ∞) at the moment of this analysis. The median TTP of patients who received bevacizumab in the first line was 11 months (95%CI 8 - + ∞). The median TTP of patients who received bevacizumab in the second+ lines was 5.5 months (95%CI 4 - + ∞) (p=0.015). The median survival time (OS) for all patients was 9 + months (95%CI 7 - + ∞). The median OS at the moment of analysis was 11 months (95%CI 9 - + ∞) for patients receiving bevacizumab in the first line, and 7 months for patients receiving the drug in the second+ lines (95%CI 6 - + ∞) (p=0.024). The incidence of any toxicity grade 3-4 was less than 10%. Bevacizumab associated incidence of grade 3-4 side effects did not exceed 5%. Hypertension 5% and thromboembolism 5% were the most frequent events. Gastrointestinal perforation did not occur. There was one toxic death due to sepsis and not directly associated with bevacizumab toxicity.*

Conclusion: *Bevacizumab can safely be added to different chemotherapeutic regimens in first- and second+ line. The conferred benefit in overall survival, TTP and response rate obviously requires randomized trials.*

Key words: *Antibodies, Monoclonal; Angiogensis Inhibitors; Colorectal Neoplasms; Treatment Outcome; Antineoplastic Combined Chemotherapy Protocols; Vascular Endothelial Growth Factor A + antagonists and inhibitors*

INTRODUCTION

There are a variety of strategies that target VEGF, although VEGF blockade with monoclonal-antibodies (mAbs) is the most studied approach. Bevacizumab is an anti-VEGF, humanized mAb that is the most advanced agent of its class in clinical development. Preclinical data show that this agent is active in colorectal cancer and other types of solid tumors and is better tolerated than conventional chemotherapeutic agents (1-3). Preclinical studies have also shown that combining anti-VEGF therapy with chemotherapeutic agents results in augmented antitumor activity (4,5). The mechanism by which bevacizumab enhances the efficacy of chemotherapy is not well understood, although it has been proposed that, as tumor blood vessels are chaotic, irregular, and leaky, relatively low dose of anti-VEGF therapy "normalize" tumor vasculature, reducing intratumoral pressure and allowing better delivery of therapeutic agents to the tumor, thereby maximizing antitumor activity (6). Against this background, it was suggested that the most effective use of bevacizumab is in combination with chemotherapy.

Several studies have examined bevacizumab in combination with chemotherapy in the first- and second-line settings in patients with metastatic CRC. Phase II or III trials of bevacizumab in combination with 5-fluorouracil/leucovorin (5-FU/LV), irinotecan, and oxaliplatin are completed or ongoing (7-9). Most of those studies shows clinical benefit including benefit in survival for bevacizumab treated patients (5-7). Despite of that, there is lack of information concerning the extent to which bevacizumab can be used to treat metastatic CRC. We still need more evidence related to efficacy and safety

of bevacizumab in different settings, or sequential treatments. The aim of this study was to investigate efficacy and safety of bevacizumab plus different chemotherapy in patients with metastatic CRC.

PATIENTS AND METHODS

Patients

This was a controlled, prospective, multicentre, national cohort study. Patients with histologically verified locally advanced disease and/or metastatic colorectal adenocarcinoma, without possibility for surgical resection, were eligible for the study. The diagnosis of locally advanced or metastatic unresectable disease was based on computed tomographic (CT) scan evaluation. Only patients with measurable disease were eligible for the treatment in the study. Other inclusion criteria were: ECOG performance status 0-2, age less than 75 years, normal functions of the bone marrow (WBC $>4x10^9$/L; platelet count $>100x10^9$/L), liver (serum bilirubin level<1.5xN), and kidney (serum creatinine concentration<1.5xN), and no contraindications for the administration of drugs. Exclusion criteria were the following: brain metastases, concomitant second malignancy in the preceding 10 years except for basal cell skin cancer, treated in situ carcinoma of the cervix, uncontrolled congestive heart failure, clinically significant arrhythmia and uncontrolled angina pectoris. The criteria for second and third treatment line were: progressive disease on previous line; ECOG performance status 0-2; normal bone marrow, liver and renal function. Informed consent was obtained from all patients.

Treatment plan

Each patient, after consultation with his/her medical oncologist, was allowed to choose one of several treatments-protocols with bevacizumab which offered as a first, second or third chemotherapy line. According to patient's decision, he/she continued chemotherapy with one of the following protocols:

a) Bevacizumab plus XELOX

Patients received oxaliplatin 130 mg/m^2 in day 1 plus oral capecitabine 1000 mg/m^2 twice daily (day 1, evening, to day 15 morning), followed by bevacizumab 7.5 mg/kg, day 1. The intercycle interval was 3 weeks.

b) Bevacizumab plus FOLFOX4

Patients received oxaliplatin 85 mg/m^2 plus folinic acid 200 mg/m^2, 2-hour infusion, days 1-2; 5-FU 400 mg/m^2, IV bolus, days 1-2; 5-FU 600 mg/m^2, 22-hour continuous infusion, days 1-2. Bevacizumab was applied at the dose of 5 mg/kg, day 1. The intercycle interval was 2 weeks.

c) Bevacizumab plus XELIRI

Patients received irinotecan 180 mg/m^2 plus oral capecitabine 1000 mg/m^2 twice daily (day 1, evening, to day 15 morning), followed by bevacizumab 7.5 mg/kg, day 1. The intercycle interval was 3 weeks.

d) Bevacizumab plus Capecitabine

Patients received oral capecitabine 1250 mg/m^2 twice daily, days 1-14, plus bevacizumab 7.5 mg/kg, day 1. The intercycle interval was 3 weeks.

e) Bevacizumab plus 5FU/LV (Mayo regimen-MCR)

Patients received 5-FU (425 mg/m^2, IV bolus, days 1-5, 4-week cycle) plus folinic acid (20 mg/m^2, IV. bolus, given first, days 1-5, plus Bevacizumab 7.5 mg/kg , day 1, 4-week cycle).

Patients were treated until disease progression or until unacceptable toxicity. Full doses of anticancer drugs were given if the leukocyte count was $4x10^9$/L and if platelet count was greater than $100x10^9$/L. When the leukocyte and platelet count were less than this, treatment was delayed for 1 week or until complete recovery occurred. If grade 2 and 3 mucositis, diarrhea or proteinuria occurred, treatment was delayed by 1 week or until normalization. For grade 4 mucositis, diarrhea or proteinuria treatment had to be discontinued. In the case of hemorrhage or thromboembolism further treatment was stopped.

Assessments

Prior to chemotherapy, the following examinations, related to the disease extension, were performed: clinical examination; endoscopic examination, imaging by various techniques (CT scan of intra-abdominal, pelvic, retroperitoneal, intrahepatic masses, chest X-ray and/or CT scan for lung/mediastinal lesions); serum biochemistry including liver function tests and peripheral blood count. Other examinations were performed optionally. All examinations relevant to the disease extension and size of the individual lesions were performed following every second cycle. Serum biochemistry was performed on days 1 and 8 of each cycle. Peripheral blood counts were performed on the same days and once weekly during the intercycle interval. In cases of hematological toxicity grades 3 or 4, peripheral blood count was performed every day until recovery from the nadir. In the cases of non-hematological toxicities grades 3-4, serum biochemistry was performed once weekly until recovery. Patients receiving at least two (MCR), three (XELOX, XELIRI, capecitabine) or four cycles (FOLFOX4) were evaluable for response rate, time to progression and survival. Treatment response was evaluated every second (MCR), every third (XELOX, XELIRI, capecitabine) or fourth (FOLFOX4) cycle according to the RECIST criteria (10). If CR was achieved, two additional courses should be administered and the patient strictly monitored thereafter. Patients with partial remission (PR) or stable disease (SD) were treated until progression. In the case of progressive disease (PD), they received the next chemotherapy line or best supportive care. After active treatment, each patient had regular follow-up on every 2 months until death.

Standard criteria were used for toxicity grading (11).

Independent response review was performed by members (surgeon, medical oncologist, radiologist and pathologist) of the joint interdisciplinary committee for gastro-intestinal tumors of the host institutions, who were not involved in the study.

Statistics

The time to progression was calculated from the start of treatment to the date when the disease progression was first noted. Survival was calculated from the start of treatment to death. Response rate was calculated on an intention-to-treat basis. Statistical analysis included Kaplan-Meier method for estimation of overall survival and time to progression and the log-rank test to assess the differences in overall survival and time to progression between the treatment groups.

RESULTS

From April 2004 to September 2006, a total of 30 consecutive patients were enrolled into the study. This includes all the patients who received bevacizumab in Serbia during this period. Patients were treated in seven institutions: Institute for Oncology and Radiology - Belgrade, Military Medical Academy - Belgrade, Oncology Institute of Vojvodina - Sremska Kamenica, KBC Bežanijska Kosa - Belgrade, University Clinic for Oncology - Niš, University Clinic for Oncology - Kragujevac, Nova Vita hospital - Belgrade.

The median follow-up is 8 months (range: 7-28+ months). All the patients

had measurable disease on CT scan. Patient characteristics are listed in Table 1. Thirty percent of all patients had performance status 2. Extent of the disease at the start of treatment is shown in Table 2. Predominant site of metastases was liver. Eighty percent of patients had previous surgery of the primary tumor. Six (20%) of patients received previous adjuvant chemotherapy. Most patients (53.3%) received bevacizumab plus chemotherapy in the first-line end the regimen most frequently combined with bevacizumab was the XELOX regimen (46.6%).

Table 1. Patient characteristics

No. of patients	30
Median age (range)	58 (37-74)
Males/Females	20/10
Performance status (ECOG)	
0	12
1	9
2	9
Sites of primary tumor	
Colon	18
Rectum	12

Table 2. Extent of disease

	N	%
Primary tumor	6	20
Local relapse	4	13.3
Liver	24	80
Lung	9	30
Lymph nodes	8	26.6
Peritoneum	5	16
Bone	2	7
Others	3	10

All patients received at least at least two (MCR), three (XELOX, XELIRI, capecitabine) or four cycles (FOLFOX4) of therapy, and all of them have been analyzed on intention-to-treat basis.

Tumor response

Objective tumor response (Table 3) was seen in 11 patients (37%) (95%CI 19-69%). The median duration of response was 12 months. Three out of 11 patients (27%) with PR had secondary surgery. They have achieved maximal response after 6, 10 and 12 months of treatment. Two of them had liver metastases and one of them had liver and lung metastases. Primary tumor was resected previously. Successful resection of metastases was performed in all three patients and they are in the no-evidence-of-disease stage at the moment of this analysis.

Objective tumor response (ORR) was seen in 9 out of 16 patients (56%) who received bevacizumab in the first line treatment (Table 4) in comparison to 2 out of 14 patients (14%) who received it in the second+ lines. There was a significant difference in response rate (Chi Square Test; p=0.02) between these subpopulations.

Clinical benefit

Clinical benefit (patients with CR+PR+SD) was seen in 22 (74%) patients treated with bevacizumab in all therapy lines together. Percent of patients who achieved clinical benefit is similar in subpopulation who received bevacizumab in the first line (75%) and in the second+ lines (71%) (Table 4).

Table 3. Treatment results – all patients

Response	No. of cases N=30	%
Partial response	11	37
Stable disease	11	37
Progressive disease	8	26
Overall response rate	11	37
(95% confidence interval)		(19-69)

Table 4. Treatment results according to the line of chemotherapy in which bevacizumab was applied

	First line		Second + … line	
Response	No. of cases N=16	%	No. of cases N=14	%
Partial response	9	56	2	14
Stable disease	3	19	8	57
Progressive disease	4	25	4	29
Overall response rate	9	56	2	14
Clinical benefit	12	75	10	71

Time to progression (TTP)

At the moment of analysis the median time to progression was 9 + months (95%CI 7 - + ∞). The median time to progression of patients who received bevacizumab in the first line was 11 months (95%CI 8 - + ∞), while in patients receiving it in the second or later lines it was 5.5 months (95%CI 4 - + ∞). There was significant difference in time to progression between those two subpopulations in favor of patients who received bevacizumab in the first-line (Log-rank test; p=0.015)

Survival (OS)

The median survival time at the moment of the analysis was 9 + months (95%CI 7 - + ∞). The median survival of patients who received bevacizumab in the first-line was 11 months (95%CI 9 - + ∞), and in patients who received bevacizumab in the second or later lines was 7 months (95%CI 6 - + ∞). There was significant difference in survival between those two subpopulations in favor of patients who received bevacizumab in the first-line (Log-rank test; p=0.024).

Toxicity

A total of 261 cycles were applied. The median number of applied cycles per patient was 8 (range 2-16). The incidence of any toxicity grade 3-4 was less than 10%. Myelosuppression was the most frequent side effect. Neutropenia grades 3 and 4 were observed in 21 (8%) cycles. We recorded 16 febrile episodes during the nadir. Four patients with febrile neutropenia developed sepsis. One of them died from septic shock despite of antimicrobial therapy. This patient did not develop bevacizumab related toxicity like bleeding, thromboembolism or gastrointestinal perforation. All other patients who had febrile neutropenia recovered from neutropenia completely. Thrombocytopenia grade 3-4 was recorded in 13 (5%) cycles. No hemorrhagic syndrome was observed related to thrombocytopenia. Anemia grade 3-4 was occurred in 10 cycles (4%). The most common non-hematological side effects grade 3-4 were nausea/vomiting (6%), diarrhea (7%), mucositis (4%) and elevation

Table 5. Toxicity

	N=261 cycles					
Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3-4 (%)
Hemoglobin	205	32	14	7	3	10 (4)
Granulocytes	193	31	16	15	6	21 (8)
Platelets	167	49	32	11	2	13 (5)
Nausea/vomiting	179	52	14	14	2	16 (6)
Diarrhea	135	70	38	13	5	18 (7)
Mucositis/Stomatitis	172	57	23	8	1	9 (4)
Creatinine	245	12	4	0	0	0 (0)
Alopecia	147	49	5	0	0	0 (0)
Bilirubin	190	47	22	2	0	2 (1)
Transaminases	183	41	29	8	0	8 (3)
Alkaline phosphatase	177	69	12	3	0	3 (1)
Heart-rhythm/function	232	17	12	0	0	0 (0)
Hypertension	197	31	19	14	0	14 (5)
Any thrombotic event	209	24	15	13	0	13 (5)
Pulmonary embolus	261	0	0	0	0	0 (0)
Bleeding	233	17	6	5	0	5 (2)
Proteinuria	196	36	21	8	0	8 (3)
Gastrointestinal perforation	261	0	0	0	0	0 (0)
Sensory neuropathy	171	61	24	5	0	5 (2)

of transaminases (3%). Non-hematological side effects had usually been of short duration, reversible and easy for management. Side effects are presented in Table 5. Bevacizumab associated incidence of grade 3-4 side effects did not exceed 5%. Hypertension (5%) and thromboembolism (5%) were the most frequent of those. Gastrointestinal perforation did not occur.

DISCUSSION

The results of this study appear to provide support for the use of bevacizumab in the treatment of advanced CRC. We found that the addition of bevacizumab to all chemotherapy lines in our cohort resulted in 37% RR and 74% of clinical benefit. At the moment of analysis median OS and TTP have not been reached, but both are exceeding 9 months. A subgroup analysis showed that the application of bevacizumab plus chemotherapy in the first-line significantly increased RR, TTP and OS with comparison to its application in the second- or following lines of chemotherapy. Response rate of 56%, and median TTP and OS surpassing 11 months were achieved in subgroup of patients who received bevacizumab with chemotherapy in the first-line. This result suggests that bevacizumab should be used upfront rather than in second-line. Clinical benefit of 71%, however, also allows bevacizumab use for patients who receive chemotherapy in the second or followed chemotherapy lines. Hurwitz and colleagues examined bevacizumab in combination with IFL as first-line chemotherapy for patients with metastatic CRC (7). The addition of bevacizumab to IFL resulted in a significantly longer survival time, by almost 5 months, and also resulted in a significantly greater overall response rate, duration of response, and progression free survival. Survival benefit was observed in all patients subgroups and was independent of the second line therapy.

Phase II and III studies have evaluated the addition of bevacizumab to 5FU/LV for the first-line treatment of metastatic CRC (8,9). These studies showed that bevacizumab/5FU/LV compares favorably with 5FU/LV. Only one patient in our study was treated with bevacizumab/5FU/LV, but we have treated a subgroup of patients with bevacizumab/capacitabine, predominately in the third line of treatment. Treatment outcome, especially clinical benefit, achieved in this subgroup of patients suggests that bevacizumab/capecitabine could be considered for patients who are resistant to irinotecan or oxaliplatin or for whom irinotecan or oxaliplatin based therapy is not recommended.

Clinical trials are in progress or being planned to evaluate the addition of bevacizumab to oxaliplatin based therapy. A recently completed phase III trial evaluated the addition of bevacizumab to FOLFOX in the second line treatment of patients who have failed previous irinotecan plus 5FU therapy (12). Data analyses demonstrated that patients receiving bevacizumab plus FOLFOX had 17% longer survival time then those receiving FOLFOX alone.

This clinical benefit achieved in our study was accompanied by relatively modest side effects of treatment, which were easily managed. The overall incidence of side effects grade 3-4 was 2-8%, attributable largely to hematological toxicity, diarrhea, hypertension requiring treatment and thrombotic events. The toxic events in our study were not significantly increased by the addition of bevacizumab to chemotherapy in comparison to chemotherapy alone reported in the literature (7-9,12).

In summary, bevacizumab can safely be added to different chemotherapeutic regimens in first- and second+ line. The conferred benefit in overall survival, time to progression and response rate obviously require a randomized approach.

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Conflict of interest

We declare no conflicts of interest.

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