

Efficacy and Toxicity of Bevacizumab on Combination with Chemotherapy in Different Lines of Treatment for Metastatic Colorectal Carcinoma

IGOR KISS¹, ZBYNEK BORTLICEK², BOHUSLAV MELICHAR³, ALEXANDR POPRACH¹, JANA HALAMKOVA¹, ROSTISLAV VYZULA¹, LADISLAV DUSEK² and TOMAS BUCHLER⁴

¹Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic;

²Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic;

³Department of Oncology, Palacky University Medical School and Teaching Hospital, Olomouc, Czech Republic;

⁴Department of Oncology, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic

Abstract. *The aim of the present study was to describe treatment outcomes for bevacizumab in combination with chemotherapy based on data from the Czech registry of targeted therapies for metastatic colorectal cancer (mCRC). Patients and Methods: In total, 4,487 patients with mCRC who received bevacizumab combined with chemotherapy in first line (n=3,990, 88.9%), second line (n=386, 8.6%), or third/higher line (n=111, 2.5%) had evaluable data and were included in the present retrospective analysis. Results: The median progression-free survival (PFS) was 11.3 months (95% confidence interval [CI]=11.0-11.7 months), 9.5 months (95% CI=8.2-10.9 months), and 7.3 months (95% CI=5.9-8.7 months; p<0.001), and the median overall survival from the start of bevacizumab-containing therapy was 28.4 months (95% CI=27.1-29.8 months), 25.9 months (95% CI=19.4-32.4 months), and 15.0 months (95% CI=10.7-19.3 months; p<0.001), respectively. Conclusion: The data describe efficacy of bevacizumab with chemotherapy for different treatment lines in a large patient cohort.*

Colorectal cancer (CRC) is one of the most common types of cancers in the developed world. In the Czech Republic, over 8,000 new cases of CRC are diagnosed yearly. Approximately one quarter of the patients have distant metastases at the time of diagnosis and another 20-25% will develop metastatic cancer (mCRC) later in the course of the

Correspondence to: Dr. Tomas Buchler, Department of Oncology, First Faculty of Medicine, Charles University and Thomayer Hospital, 140 59 Prague, Czech Republic. Tel: +420 261082637, Fax: +420 261082522, e-mail: tomas.buchler@ftn.cz

Key Words: Colorectal cancer, metastasis, bevacizumab, chemotherapy, survival.

disease. Targeted agents in combination with 5-fluorouracil (5-FU)-based regimens containing oxaliplatin or irinotecan constitute the standard therapy for metastatic disease. Targeted drugs increase the overall response rate and the likelihood of conversion of inoperable to operable metastatic disease, and prolong survival.

Bevacizumab is a humanized recombinant monoclonal antibody directed at vascular endothelial growth factor A. Based on a number of clinical studies, bevacizumab was registered in combination with fluoropyrimidine-based chemotherapy for the treatment of mCRC in the first as well as second or higher lines of therapy.

Although bevacizumab is now routinely used for many patients with mCRC, the proper positioning of the drug in the treatment sequence has been subject to many discussions and controversies. The present study aims to analyze the efficacy and safety of bevacizumab/chemotherapy combination in the first, second, and third/higher lines of treatment based on data from a national registry.

Patients and Methods

Data source. The data for this retrospective analysis were obtained from the national registry of patients treated with targeted agents for colorectal cancer. The CORECT registry (<http://corect.registry.cz/>) is a non-interventional post-registration database collecting epidemiological and clinical data of patients with mCRC treated with targeted therapies including bevacizumab, cetuximab, panitumumab, and regorafenib in the Czech Republic. The reimbursement of these treatments from public health insurance in the Czech Republic is limited to a network of comprehensive cancer centers entering anonymized patient data into the registry. The CORECT registry is estimated to cover approximately 90% of patients treated with bevacizumab outside clinical studies. The individual patient data including demographic parameters, initial staging, and disease characteristics, data on used targeted therapy, survival, and adverse events are continuously entered into the registry and updated at least twice a year.

Table I. Baseline characteristics of analysed patients.

Characteristic	Systemic therapy line			Total (n=4487)
	First (n=3,990)	Second (n=386)	Third and higher (n=111)	
Males, n (%)	2,499 (62.6)	250 (64.8)	75 (67.6)	2,824 (62.9)
Age at treatment initiation, (years) median (range)	61.9 (20-88)	63.3 (30-84)	62.2 (30-84)	62.0 (20-88)
Localization, n (%)				
Colon	2,438 (61.1)	215 (55.7)	57 (51.4)	2,710 (60.4)
Rectum	1,552 (38.9)	171 (44.3)	54 (48.6)	1,777 (39.6)
History of thromboembolism, n (%)	160 (4.0)	18 (4.7)	6 (5.4)	184 (4.1)
History of hypertension, n (%)	1,500 (37.6)	160 (41.5)	25 (22.5)	1,685 (37.6)
Primary metastatic, n (%)				
M0	1,512 (37.9)	204 (52.8)	55 (49.5)	1,771 (39.5)
M1	2,478 (62.1)	182 (47.2)	56 (50.5)	2,716 (60.5)
Adenocarcinoma, n (%)	3,881 (99.3)	369 (98.7)	103 (98.1)	4,353 (99.2)
Prior surgery, n (%)	3,250 (81.5)	329 (85.2)	83 (74.8)	3,662 (81.6)
Radiotherapy of primary tumour, n (%)	796 (19.9)	127 (32.9)	29 (26.1)	952 (21.2)
Adjuvant chemotherapy, n (%)	1,213 (30.4)	193 (50.0)	53 (47.7)	1,459 (32.5)
Bevacizumab treatment duration (months) median (5%-95%)	6.7 (1.1-20.6)	5.7 (1.1-20.1)	4.8 (1.2-13.1)	6.4 (1.1-20.5)
Best response in patients who completed bevacizumab treatment, n (%)				
ORR (CR+PR)	1,321 (42.9)	112 (34.0)	8 (8.3)	1,441 (41.1)
CR	412 (13.4)	26 (7.9)	1 (1.0)	439 (12.5)
PR	909 (29.5)	86 (26.1)	7 (7.3)	1,002 (28.6)
SD	1,149 (37.3)	118 (35.9)	44 (45.8)	1,311 (37.4)
PD	413 (13.4)	76 (23.1)	33 (34.4)	522 (14.9)
Not available	194 (6.3)	23 (7.0)	11 (11.5)	228 (6.5)

ORR, Overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Study population and treatment. Patients with mCRC treated with bevacizumab at any point during their therapy were included in the present analysis. The patient population was stratified into three groups based on the line of treatment that was administered with bevacizumab. The recommended dose of bevacizumab was 5 mg/kg intravenously (*i.v.*) every two weeks or 7.5 mg/kg *i.v.* every three weeks. The treatment continued until progression, severe toxicity, or complete resection of disease. Disease responses were assessed using the Response Evaluation Criteria In Solid Tumors (RECIST) criteria 1.1 (1).

Statistical analysis. Standard frequency tables and summary statistics were used to characterize sample data set and treatment efficacy. Efficacy of the treatment was assessed in terms of objective response rate (ORR), median progression-free survival (PFS), and overall survival (OS). Overall survival (OS) and progression-free survival (PFS) were calculated using the standard Kaplan–Meier method. PFS was defined as time from the onset of bevacizumab therapy to progression or death due to any cause. OS was defined in two ways as time from the onset of bevacizumab treatment and from time of stage IV diagnosis to death from any cause. Statistical significance of the differences in survival was assessed using the log-rank test. All estimates are accompanied with 95% confidence interval (CI). Standard level of significance $\alpha=0.05$ was used, except for comparison of separate lines of therapy where Bonferroni correction significance level of $\alpha/3=0.017$ was used.

Results

Baseline characteristics and treatment. At the time of analysis, the registry contained 4,487 complete records of patients treated with bevacizumab in combination with chemotherapy for mCRC. A summary of baseline characteristics is shown in Table I. The median age of the patients in the database was 62 years and the majority (64.8%) of patients were aged 65 years or less. The median age of patients in the sub-groups defined by the treatment line was 62 years, 63 years, and 62 years for the first, second, and third/higher line, respectively. There was a statistically significant difference in the age of the patients between the first and the second line. The most common histological tumor type was adenocarcinoma (99.2%), originating from the colon and the rectum in 60.4% and 39.6% of patients, respectively.

The most common chemotherapy regimens used in combination with bevacizumab were the oxaliplatin-based regimens with infusional 5-FU/leucovorin/oxaliplatin (FOLFOX) or capecitabine/oxaliplatin (XELOX) (42.2% and 30%, respectively). Less often, bevacizumab was combined with irinotecan-based chemotherapies including infusional 5-

FU/leucovorin/irinotecan (FOLFIRI) and capecitabine/oxaliplatin (XELIRI) (10.5% and 5.0%, respectively). Rarely, bevacizumab was combined with a single-agent chemotherapy such as capecitabine (4.4%), irinotecan or oxaliplatin, or with bolus 5-FU/leucovorin regimens including the Mayo 5-FU/folinic acid (FA) regimen or the 5-FU/FA/oxaliplatin (bFOL) combination (less than 1% each). Most patients received bevacizumab as part of the first-line regimen (88.9%). Only 8.6% and 2.5% of patients in the registry received bevacizumab in the second and third/higher-line treatment, respectively

Treatment outcomes. Median PFS was 11.1 months (95% CI=10.7-11.4 months) for the whole cohort. Median PFS in the first, second, and third/higher lines was 11.3 months (95% CI=11.0-11.7 months), 9.5 months (95% CI=8.2-10.9 months), and 7.3 months (95% CI=5.9-8.7 months), respectively (Figure 1A). This difference in PFS was statistically significant ($p<0.001$). Median OS from the start of chemotherapy/bevacizumab was 28.4 months (95% CI=27.1-29.8 months), 25.9 months (95% CI=19.4-32.4 months), and 15.0 months (95% CI=10.7-19.3 months), respectively ($p<0.001$) (Figure 1B and Table II). Median survival from diagnosis of metastatic disease was 29.2 months (95% CI=27.7-30.9 months), 37.9 months (95% CI=32.4-43.5 months), and 40.5 months (95% CI=33.9-47.0 months), respectively ($p<0.001$) (Figure 1C and Table III).

ORR of the entire population of patients who completed bevacizumab treatment was 41.1%, including complete response (CR) in 12.5% of patients and partial response (PR) in 28.6% of patients. ORR was 42.9%, 34.0% and 8.3% in the first, second, and third/higher line, respectively (Table IV). Regarding the response rate, the largest differences between the lines was observed for CR (13.4%, 7.9% and 1.0% respectively), but only a minimal difference in the PR rate was noted between the first and the second line of treatment (29.5% and 26.1%, respectively, while only 7.3% patients achieved PR in third/higher line).

Treatment toxicity. Only adverse events considered to be associated with bevacizumab are reported to the CORECT registry. The incidence of adverse events was 11.6%, 8.8%, and 8.1% for the first, second, and third/higher line, respectively. Significant (*i.e.* grade 3-5) adverse events were rarely reported (6.1%, 2.6% and 4.5%, respectively). As expected, the most common significant adverse event irrespective of the chemotherapy backbone was hypertension, occurring in 3.1%, 3.1% and 0.9%, respectively. Thromboembolic disease was reported in 2.9%, 1.3% and 1.8% of patients, and proteinuria was reported in 1.6%, 1.8% and 0.9% of patients for the different treatment lines. Grade 3 bleeding occurred in 1.2% of patients in the first line treatment, in fewer than 1% of patients in the second line,

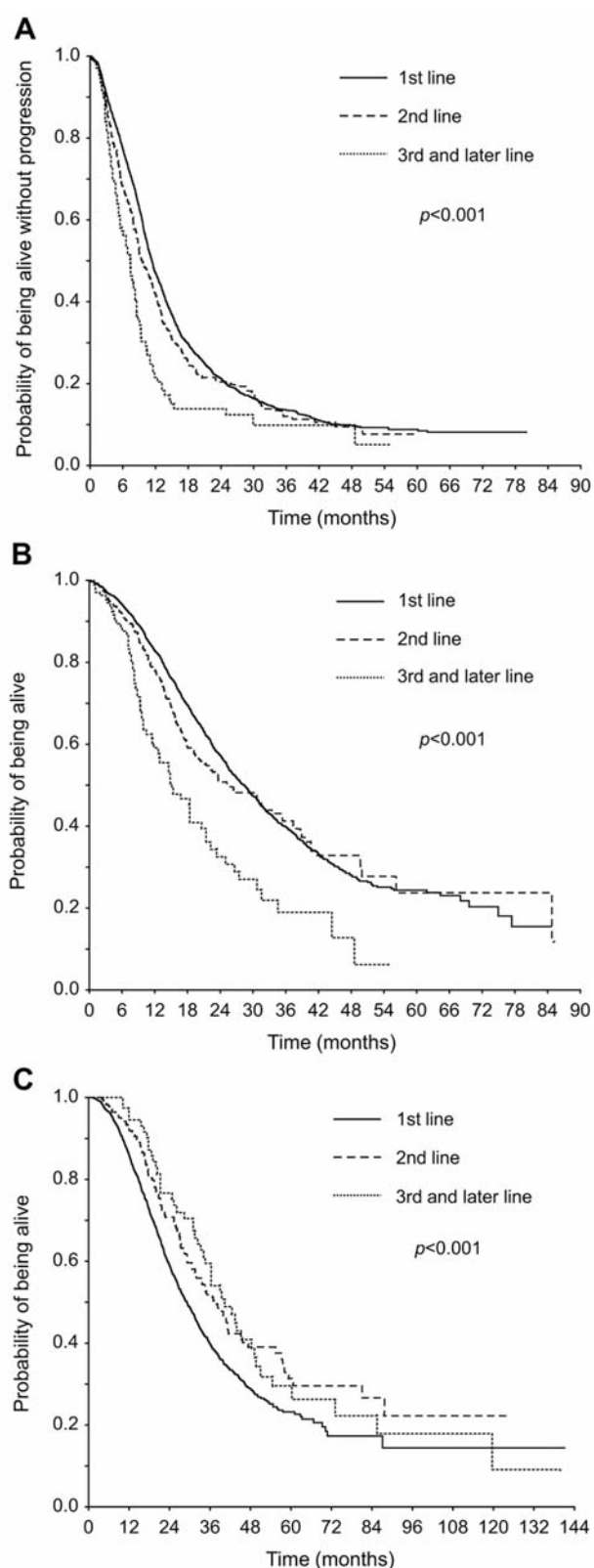


Figure 1. Progression-free (A) and overall (B) survival from bevacizumab treatment initiation, and overall survival from diagnosis of metastatic disease (C).

Table II. Overall survival (OS) and progression-free survival (PFS) analysis.

	Systemic therapy line			Log-rank test p-value
	1st (n=3,990)	2nd (n=386)	3rd and later (n=111)	
Median OS from bevacizumab treatment initiation (95% CI)	28.4 months (27.1-29.8)	25.9 months (19.4-32.4)	15.0 months (10.7-19.3)	<0.001
Median PFS from bevacizumab treatment initiation (95% CI)	11.3 months (11.0-11.7)	9.5 months (8.2-10.9)	7.3 months (5.9-8.7)	<0.001
Median OS from diagnosis of metastatic disease *(95% CI)	29.2 months (27.7-30.9)	37.9 months (32.4-43.5)	40.5 months (33.9-47.0)	-

*Only for patients with known date of stage IV diagnosis: first line: n=2921, second line: n=230, later lines: n=77; CI, confidence interval.

Table III. Overall survival (OS) and progression-free survival (PFS) analysis-comparison of different systemic treatment lines.

Log-rank test p-values	OS from bevacizumab treatment initiation		PFS from bevacizumab treatment initiation	
	1st line	2nd line	1st line	2nd line
Second line	0.172	-	0.025	-
Third and higher lines	<0.001	<0.001	<0.001	0.002

and in 1.8% patients in third/higher line. Other adverse events including diarrhea and gastrointestinal perforation were recorded in fewer than 1% of cases. The number of patients with gastrointestinal perforation was 10 in the first line and one in the second line.

Discussion

Median PFS for patients receiving bevacizumab as a part of first-line therapy for metastatic disease included in the CORECT registry is comparable to the results reported earlier in prospective randomized clinical trials and observational studies, with a median PFS in the first-line setting of approximately 8-11 months with different backbone chemotherapy regimens (2-4).

The observed median PFS is also consistent with the results of observational studies BRITE, BEAT, and ARIES (5-7). The median PFS in patients treated with combination chemotherapy with bevacizumab in the second and third/higher-line of treatment in the registry exceeded previously published results. In the second line, the median PFS of 9.5 months in the CORECT database compares favorably with median PFS of 7.3 months reported in a phase III study comparing the effect of FOLFOX chemotherapy with or without bevacizumab as a second-line treatment (8). Similarly, PFS of 8.3 and 7.8 months was reported for the FOLFIRI/bevacizumab and FOLFOX/bevacizumab cohorts in an observational study (9). A pooled analysis has also

Table IV. Best treatment responses to different lines of chemotherapy with bevacizumab.

Response	Systemic treatment line		
	1st (n=3,990)	2nd (n=386)	3rd and later (n=111)
CR	474 (11.9%)	29 (7.5%)	2 (1.8%)
PR	1,072 (26.9%)	96 (24.9%)	8 (7.2%)
SD	1,425 (35.7%)	134 (34.7%)	50 (45.0%)
PD	413 (10.4%)	76 (19.7%)	33 (29.7%)
NA	606 (15.2%)	51 (13.2%)	18 (16.2%)
Total	3,990 (100%)	386 (100%)	111 (100%)

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NA, not available.

confirmed clinically meaningful improvement of survival with bevacizumab added to chemotherapy regimens commonly used for mCRC (10).

In the third/higher-line treatment, PFS of 7.3 months of the CORECT database is again higher than the results of previously published studies including a phase II trial of 5-FU/FA/bevacizumab (median PFS 3.5 months) (11) and a retrospective study of FOLFIRI/bevacizumab and FOLFOX/bevacizumab (median PFS 5.3 months) (12).

The median OS in the first-line subgroup of the CORECT cohort is better than that reported for bolus regimens such as irinotecan/5-FU/leucovorin (IFL), modified IFL, and bFOL

(2, 3, 13) and correspond to the results published for continuous regimens such as FOLFIRI, FOLFOX, and XELOX with median OS of 28.0, 26.1 and 24.6 months, respectively. The median OS in the present analysis is also consistent with the results reported for the BRiTE, BEAT and ARIES observational studies (5-7). Although longer PFS in the first line of treatment was expected, it could have been counter-balanced by a probable selection bias for patients in later lines of therapy, as evidenced by significantly longer survival from the diagnosis of metastatic disease in patients treated in the second and the third/higher line.

OS for patients receiving bevacizumab as a part of the second line therapy in the CORECT registry was superior to that obtained with FOLFOX/bevacizumab in the E3200 study (10.8 months) (8) and in a small retrospective Korean cohort (16.6 months) (14). However, longer OS was reported in an observational study by Moriwaki *et al*. (21.6 months for FOLFIRI/bevacizumab and 16.5 months for FOLFOX/bevacizumab) (9).

Outcomes for the third/higher line of treatment are better than published results of a phase II study (median OS 9.1 months with the combination 5-FU/FA/bevacizumab) as well as results of retrospective studies using FOLFIRI/bevacizumab and FOLFOX/bevacizumab (11, 12, 14). It is, however, evident from our results that patients receiving bevacizumab as a part of the second-line, and especially the third-line treatment have favorable prognosis, which is related to the previous history of the disease. Moreover, in the CORECT database, the number of patients treated in the second or higher-line of therapy represents a small proportion of the patients, and a selection bias is probable.

The addition of bevacizumab to chemotherapy increases the incidence of bevacizumab-specific side-effects including hypertension, bleeding, perforation of the digestive tract, thromboembolic events, and significant proteinuria (15). The present registry-based retrospective analysis confirms that bevacizumab in combination with chemotherapy has a similar toxicity profile regardless of the treatment line. The data show very good tolerability to bevacizumab across the different lines of therapy.

The key strengths of the present analysis are the sample size as well as the fact that the analysis is population-based and virtually all patients with mCRC treated with bevacizumab in the Czech Republic were included. The main weak point of our study is its retrospective nature, likely resulting in a selection bias. The number of patients treated in the second and third/higher line is also disproportionate to the number of patients treated in the first line, creating problems in statistical comparisons. The response rate was based on investigator assessment, and the rather high CR rate was not verified by an independent review.

In conclusion, the present data describe the efficacy of bevacizumab/chemotherapy combinations in different lines

of treatment of mCRC and confirm that the incidence and spectrum of toxicities remains unchanged.

Funding

The maintenance of the CORECT registry is partly funded by Roche, Merck, and Amgen.

Conflicts of Interest

Dr. Kiss has received speakers' honoraria and has acted on an advisory board for Roche. Dr. Buchler has received speakers' honoraria from Roche. Professor Melichar has received speakers' honoraria and has acted on an advisory board for Roche. All other Authors state that they have no conflicts of interest.

Acknowledgements

We would like to thank the following heads of the comprehensive cancer centers for their permission to use data of patients from their respective regional networks: Dr. Václav Janovský, České Budějovice; Professor Jindřich Fínek, Plzeň; Professor Jiří Vorlíček, Brno; Dr. Lubomír Slavíček, Jihlava; Professor Renata Soumarová, Nový Jičín; Dr. Jiří Bartoš, Liberec; Dr. David Feltl, Ostrava; Dr. Jana Prausová, Prague; Dr. Milan Lysý, Ústí nad Labem; Professor Jiří Petera, Hradec Králové. We are also indebted to all physicians who provided data for the CORECT registry.

References

- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
- Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R and Kabbinavar F: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 350: 2335-2342, 2004.
- Fuchs CS, Marshall J, Mitchell E, Wierzbicki R, Ganju V, Jeffery M, Schulz J, Richards D, Soufi-Mahjoubi R, Wang B and Barrueco J: Randomized, controlled trial of irinotecan plus infusional, bolus or oral fluoropyrimidines in first line treatment of metastatic colorectal cancer: results from BICC-C study. *J Clin Oncol* 25: 4779-4786, 2007.
- Sobrero A, Ackland S, Clarke S, Perez-Carrión R, Chiara S, Gapski J, Mainwaring P, Langer B and Young S; AVIRI Trial investigators: Phase IV study of bevacizumab in combination with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) in first-line metastatic colorectal cancer. *Oncology* 77: 113-119, 2009
- Kozloff M, Yood MU, Berlin J, Flynn PJ, Kabbinavar FF, Purdie DM, Ashby MA, Dong W, Sugrue MM and Grothey A; Investigators of the BRiTE study *et al*: Clinical outcomes associated with bevacizumab-containing treatment of metastatic colorectal cancer: The BRiTE observational cohort study. *Oncologist* 14: 862-870, 2009.

- 6 Van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M, Mazier MA, Canon JL, Georgoulas V, Peeters M, Bridgewater J and Cunningham D; First BEAT investigators: Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: The BEAT study. *Ann Oncol* 20: 1842-1847, 2009.
- 7 Bendell JC, Bekaii-Saab TS, Cohn AL, Hurwitz HI, Kozloff M, Tezcan H, Roach N, Mun Y, Fish S, Flick ED, Dalal D and Grothey A: Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-Bevacizumab or FOLFIRI-Bevacizumab: Results from ARIES, a Bevacizumab observational Cohort Study. *Oncologist* 17: 1486-1495, 2012.
- 8 Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA and Benson AB 3rd; Eastern Cooperative Oncology Group Study E3200: 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* 25: 1539-1544, 2007.
- 9 Moriwaki T, Bando H, Takashima A, Yamazaki K, Esaki T, Yamashita K, Fukunaga M, Miyake Y, Katsumata K, Kato S, Satoh T, Ozeki M, Baba E, Yoshida S, Boku N and Hyodo I: Bevacizumab in combination with irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) in patients with metastatic colorectal cancer who were previously treated with oxaliplatin-containing regimens: a multicenter observational cohort study (TCTG 2nd-BV study). *Med Oncol* 29: 2842-2848, 2012.
- 10 Popov I, Milicević M and Radosević-Jelić LJ: The addition of bevacizumab to fluoropyrimidine, irinotecan and oxaliplatin-based therapy improves survival for patients with metastatic colorectal cancer (CRC): combined analysis of efficacy. *Acta Chir Jugosl* 55: 11-6, 2008.
- 11 Chen HX, Mooney M, Boron M, Vena D, Mosby K, Grochow L, Jaffe C, Rubinstein L, Zwiebel J and Kaplan RS: Phase II multicenter trial of bevacizumab plus fluoropyrimidines and leucovorin in patients with advanced refractory colorectal cancer: An NCI Treatment Referral center Trial TRC-0301. *J Clin Oncol* 24: 3354-3360, 2006.
- 12 Kang BW, Kim TW, Lee JL, Ryu MH, Chang HM, Yu CS, Kim JC, Kim JH, Kang YK and Lee JS: 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: A retrospective analysis. *Med Oncol* 26: 32-37, 2009.
- 13 Hochster HS, Hart LL, Ramanathan RK, Childs BH, Hainsworth JD, Cohn AL, Wong L, Fehrenbacher L, Abubakr Y, Saif MW, Schwartzberg L and Hedrick E: Safety and efficacy of oxaliplatin and fluoropyrimidines regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer. Results of the TREE Study. *J Clin Oncol* 26: 3523-3529, 2008.
- 14 Park LC, Lee HS, Shin SH, Park SJ, Park MI, Oh SY, Kwon HC, Baek JH, Choi YJ, Kang MJ and Kim YS: Bevacizumab as a second- or later-line of treatment for metastatic colorectal cancer. *World J Gastroenterol* 18: 1104-1109, 2012.
- 15 Macedo LT, da Costa Lima AB and Sasse AD: Addition of bevacizumab to first-line chemotherapy in advanced colorectal cancer: a systematic review and meta-analysis, with emphasis on chemotherapy subgroups. *BMC Cancer* 12: 89, 2012.

Received December 8, 2013

Revised December 23, 2013

Accepted December 27, 2013