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ORIGINAL ARTICLE

Safety and tolerability of first-line bevacizumab in metastatic colorectal cancer

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Summary

Purpose: *To determine the clinical features of bevacizumab-associated toxicities in metastatic colorectal cancer (MCRC) patients.*

Methods: *The medical records of 60 patients with MCRC who were treated with chemotherapy including bevacizumab in the first-line setting were retrospectively evaluated.*

Results: *Bevacizumab was administered along with irinotecan plus 5-fluorouracil/leucovorin (5-FU/LV) to 44 patients, 5-FU/LV+oxaliplatin to 8 patients, capecitabine+oxaliplatin to 6 patients and 5-FU/LV to 2 patients. The total number of the cycles received was 381 (median 6, range 1-13). The most common bevacizumab-related toxicity was grade 1-2 bleeding (28%) followed by hypertension (17%). Grade 1-2 proteinuria was seen in 8% of the patients (no grade 3-4 proteinuria). Arterial thromboembolic events (ATE) were not observed, however 3 patients (5%) had experienced grade 3-4 venous thromboembolic events. In 3 patients (5%) grade 1-2 wound complications were seen (delayed wound healing in the place of the venous access device in 2, and wound infection in 1). In addition, gastrointestinal perforation (GIP) was seen in 3 (5%) patients. Two of the patients were treated by surgical intervention and one patient died of sepsis.*

Conclusion: *Bevacizumab is well tolerated when combined with various chemotherapy regimens. As bevacizumab is becoming widely used in the routine oncology practice, further studies which investigate the mechanism of bevacizumab-associated toxicities are warranted to develop effective management strategies for these adverse events.*

Key words: bevacizumab, bleeding, colorectal cancer, gastrointestinal perforation, hypertension, thromboembolism

Introduction

Investigating the role of angiogenesis in tumor growth and proliferation provides clues for the development of targeted therapies against various molecules involved in this process. One of the target molecules is vascular endothelial growth factor (VEGF), which is a basic mediator of angiogenesis. Among the VEGF family members (VEGF-A, B, C and D) VEGF-A plays a principal role in angiogenesis [1]. Bevacizumab which is the first developed monoclonal humanized IgG1 antibody, inhibits endothelial cell proliferation and new vessel formation through binding to VEGF-A [2]. Bevacizumab was approved by the FDA in February 2004 for use in the first-line treatment in MCRC patients after it was proven that addition of bevacizumab to 5-FU-based chemotherapy resulted in significant improvement of overall survival (OS), progression free survival (PFS) and response rates compared with non-bevacizumab containing chemotherapy [3]. Later, newer studies revealed its efficacy in second-line treatment [4]. Now, bevacizumab is widely used for first- and second-line treatment with chemotherapy as a standard regimen.

Adverse events associated with bevacizumab have been commonly reported as a result of the wide use of this agent. Bevacizumab-related adverse events are hypertension, proteinuria, GIP and bleeding, arterial and venous thromboembolism and wound complications [5]. Phase II and III studies have shown that hy-

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pertension and proteinuria are minor effects, but thromboembolism, hemorrhage and GIP could be fatal [5].

In this retrospective study, we analysed the adverse events attributable to bevacizumab in MCRC patients who received first-line chemotherapy, and discussed our results with the results of similar published studies.

Methods

The medical records of 166 patients with MCRC who had been treated in our clinic between December 2007 and May 2009 were retrospectively studied and the data of 60 patients who had been administered first-line chemotherapy along with bevacizumab were further analysed. Patient age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary tumor location, metastatic sites and chemotherapy regimens were analyzed. In addition, adverse events due to chemotherapy (leukopenia, neutropenia, anemia, thrombocytopenia, nausea, vomiting, diarrhea, mucositis, neuropathy, and hand-foot syndrome) and bevacizumab-related side effects (hypertension, bleeding, proteinuria, venous and arterial thrombotic events, GIP, and wound complications) were studied. The bevacizumab dose was 5 mg/kg every 2 weeks in 5-FU-based regimens [irinotecan plus 5-FU/leucovorin (5-FU/LV), 5-FU/LV+oxaliplatin, and 5-FU/LV] or 7.5 mg/kg every 3 weeks in capecitabine-based regimens (capecitabine+oxaliplatin).

Statistical considerations

SPSS for Windows (version 13.0) software program was used for evaluation of study data and statistical analysis. For the evaluation of variables (age, sex, performance status, tumor characteristics, chemotherapy regimens and adverse events) descriptive statistics and frequency analysis were performed. Shapiro-Wilk test was used to determine whether variables are normally distributed or not. Arithmetic mean was used for the measurement of central tendency of normally distributed variables, whereas median was used for the central tendency of non-normally distributed variables.

Results

The baseline patient characteristics are shown in Table 1. Nearly all patients (95%) had ECOG performance status 0-1. Thirty-three percent of the patients had more than 2 metastatic sites and liver and lung were the most common metastatic locations. The most common used chemotherapy regimen was FOLFIRI (73%). In total, 381 cycles of chemotherapy were administered (median 6 cycles, range 3-15). The median duration of follow-up was 20.2 months (range 6.2-49.5).

Toxicity data are summarized in Table 2. While no toxicities were reported in 11 patients (18.3%), grade 3-4 toxicities were observed in 25 patients (41.6%). The most commonly seen grade 3-4 adverse events were neutropenia and nausea/vomiting/diarrhea. Febrile neutropenia was not reported in any of the patients.

Adverse events associated with bevacizumab are displayed in Table 3. Hypertension was seen in 10 (16.6%) patients, with grade 3 in 4 of them. Eight of the 10 patients had known hypertension history. All hypertension episodes had been treated easily with standard anti-hypertensive agents (angiotensin-converting enzyme inhibitors, diuretics, calcium channel blockers).

Bleeding was seen in 17 (28.3%) patients; 16 of

Table 1. Baseline characteristics of patients treated with bevacizumab plus chemotherapy

Characteristics	*N (%)*
Number of patients	60 (100)
Mean age, years (range)	60 (30-87)
Sex	
Male	34 (57)
Female	23 (43)
ECOG performance status	
0	27 (45)
1	30 (50)
2	3 (5)
Primary tumor location	
Colon	37 (62)
Rectum	23 (38)
Number of metastatic sites	
≤2	40 (67)
>2	20 (33)
Metastatic sites	
Liver	41 (68)
Lung	17 (28)
Lymph nodes	14 (23)
Peritoneum	11 (28)
Bone	6 (10)
Ovary	3 (5)
Adrenal	2 (3)
Other	4 (7)
Chemotherapy regimen	
FOLFIRI	44 (73)
FOLFOX	8 (13)
XELOX	6 (10)
5-FU/LV	2 (3)

Table 2. Grade 3-4 adverse events related with chemotherapy only

Adverse events	*Grade 1-2 N (%)*	*Grade 3-4 N (%)*
Hematologic		
Leukopenia	20 (33)	3 (5)
Neutropenia	15 (25)	7 (12)
Anemia	28 (47)	2 (3)
Thrombocytopenia	12 (20)	1 (2)
Non-hematologic		
Nausea	21 (35)	5 (8)
Vomiting	4 (7)	4 (7)
Diarrhea	16 (27)	5 (8)
Mucositis	8 (13)	1 (2)
Neuropathy	8 (13)	–
Hand-foot syndrome	–	–

Table 3. Bevacizumab-related adverse events

Adverse events	*Grade 1-2 N (%)*	*Grade 3-4 N (%)*
Hypertension	6 (10)	4 (7)
Bleeding	17 (28)	–
Proteinuria	5 (8)	–
Venous thrombotic event	–	3 (5)
Arterial thrombotic event	–	–
Gastrointestinal perforation	3 (5)	–
Wound complications	3 (5)	–

them had epistaxis, and one hematuria. Gastrointestinal hemorrhage was not observed. All bleeding episodes were grade 1-2. Bleeding occurred after the first cycle of treatment in 12 of these 17 patients, re-bleeding was observed in only 4 patients.

Proteinuria was registered in 5 patients; in all of them it was grade 1-2, 4 of them had a history for hypertension, and trace protein in their initial urinalysis had been reported before chemotherapy. There was no increase in the amount of proteinuria during follow-up.

ATE were not observed, but venous thrombotic events developed in 3 patient (acute pulmonary embolism in 2 and deep venous thrombosis in 1). All 3 patients had been successfully treated with anti-coagulant agents and recurrent embolism was not seen.

Wound complications were seen in 3 patients; 2 of them had delayed wound healing (Figure 1), and 1 developed wound infection. Treatment continued without any further complication after a brief interruption of 1-2 weeks in all of these patients.

GIP was seen in 3 (5%) patients. Two of them were free perforations (Figure 2) and in 1 patient there was development of rectovaginal fistula. FOLFIRI was the chosen chemotherapy regimen in all 3 patients. Perforation occurred at the 7th month of treatment (after 12 cycles) in 2 patients and at the 5th month (after 9 cycles) in 1 patient. Two patients had been treated successfully with surgery, but 1 patient died due to sepsis.

Twenty-three percent of the patients experienced at least one adverse event requiring hospitalization. The most commonly seen adverse event which caused temporary treatment interruption was neutropenia (7 patients). The others were vomiting (3 patients), vomiting and diarrhea (1 patient), diarrhea (4 patients), GIP (3 patients) and venous thrombotic complications (3 patients). Bevacizumab-related adverse events were 22% of all the adverse events which caused treatment interruption. Eleven (18.3%) patients had died; in 10 of them death was associated with disease progression, and in 1 to an adverse event (GIP). Sixty-day mortality rate was 5%.

Discussion

Bevacizumab-related adverse events and their outcomes were investigated in this retrospective study. We found that bevacizumab is well-tolerated while it can be used in combination with various chemotherapeutic regimens. Although our study included a limited number of patients, bevacizumab-related toxicities were low compared with other published relevant clinical trials.

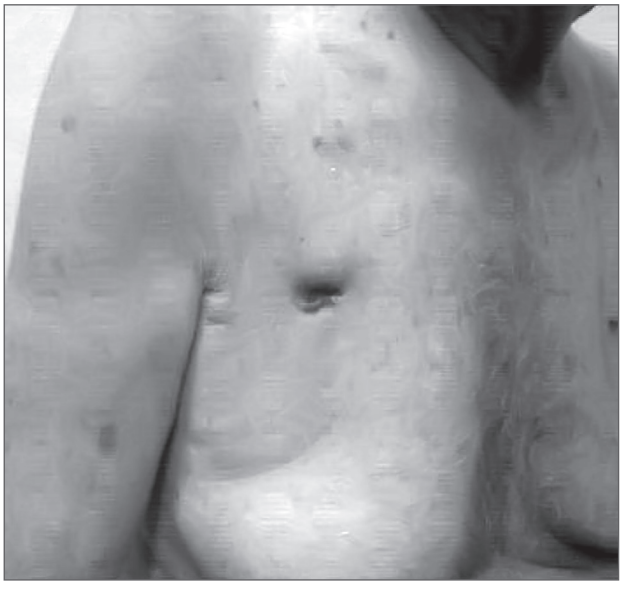

Figure 1. Wound healing failure and dehiscence in the port incision region.

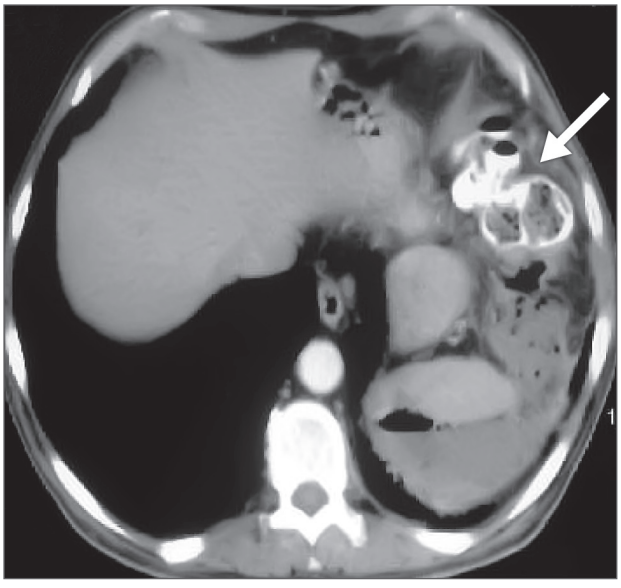

Figure 2. Gas and extraluminal contrast material at the splenic flexure level (arrow) demonstrates free perforation.

Kabbinavar et al. designed the first trial in 2003 which they combined bevacizumab and 5-FU-based chemotherapy [6]. In that phase II study FU/LV alone, low dose and high dose bevacizumab in combination with FU/LV were compared for efficacy and safety in 104 patients with MCRC. Bevacizumab in combination with chemotherapy produced distinct and statistically important improvement in PFS and OS. Thrombosis, hypertension, proteinuria, epistaxis, headache, fever and rash were described as bevacizumab-related toxicities in the safety analysis. Under the light of this study, a phase III study with 813 patients designed by Hurwitz et al. in 2004 discovered that using bevacizumab in combination with irinotecan, 5-FU and leucovorin (IFL) improved response rate, PFS and OS compared with IFL alone [3]. In this study the first GIP cases associated with bevacizumab were reported. Hypertension, proteinuria, thrombotic events, bleeding and GIP are the most commonly seen adverse events described in previous clinical studies [4-13].

An analysis of bevacizumab-related toxicities in randomized trials of bevacizumab in MCRC is listed at Table 4. Although case numbers and chemotherapy regimens were different, grade 3-4 adverse event rates varied from 51 to 87%, but serious adverse events that required discontinuation of treatment were low (8-30%) [3,6-8,10-15]. The incidence of grade 3-4 adverse events were higher in patients receiving bevacizumab when compared to patients not receiving the agent. This might be explained by the fact that patients who received bevacizumab lived longer and therefore they were exposed to more cycles of treatment [3,6]. Increased incidence of grade 3 hypertension may be the reason of higher rate of serious adverse events. Several authors have reported that grade 3-4 adverse event rates capable to cause treatment discontinuation or hospitalization were higher in bevacizumab plus chemotherapy groups compared with chemotherapy without bevacizumab, but the difference did not reach statistical significance [3,6,9]. Furthermore, nearly all of the adverse events requiring treatment interruption were of grade 1-2 and mostly associated with chemotherapy (neutropenia or diarrhea) [3,12]. In our study grade 3-4 adverse events were seen in 36.6% of the patient population. Although the adverse event rate seems to be low compared with the literature data, this could be attributed to the relatively small number of patients, their PS and the presence of 2 or less metastatic sites in the majority of the subjects who were included in the study. Bevacizumab-related events constituted 22% of the adverse events requiring treatment discontinuation and 42% requiring hospitalization.

Hypertension is the most commonly seen adverse event associated with bevacizumab in several studies [3,7-9]. Generally it is of grade 1 or 2 and its incidence varies from 19 to 34%. Grade 4 hypertension which causes treatment interruption is less than 1% [3,5,7,12,13,15]. While the exact mechanism of hypertension is not known, its suggested that alteration in nitric oxide signaling, increased plasminogen activator-1 (PAI-1) and increased vascular resistance are possible mechanisms [16]. Risk factors for hypertension are also not known, but it seems to be dependent on the dosage. Older age can also be identified as another risk factor, but findings are controversial. In a large observational study (Bevacizumab Regimens Investigation of Treatment Effects and Safety [BRITE]) there was no difference between patients older or younger than 65 years in relation to hypertension incidence [5]. In another study with 60 patients, grade 3 hypertension was seen in 29% of patients older than 75, in 11% of those aged 70-74, and in 10% of patients 65-69 years old [17].

Hypertension was registered in 16.6% (n=10) cases in our study and grade 3 hypertension was seen only in 4 patients. Eight of these 10 patients had known hypertension history, and 6 were older than 65 years. Blood pressure control was achieved in all patients with standard anti-hypertensive drugs. We think that careful blood pressure monitoring must be held in patients with hypertension history and older than 65 years of age while using bevacizumab.

In our study bleeding was the most commonly seen bevacizumab-related adverse event in the form of grade 1 epistaxis (28%). Gastrointestinal bleeding, vaginal bleeding and CNS bleeding have been reported [17], yet in our study no grade 3-4 bleeding was noted. In the AVF0780 trial, epistaxis was seen in 11% of patients in the chemotherapy-alone group, in 46% in the 5 mg/kg bevacizumab group and in 53% in the 10 mg/kg bevacizumab group, all of them grade 1 [6]. Gastrointestinal bleeding was not seen in the chemotherapy-alone group, but it was registered in 7 patients in the bevacizumab group. In the AVF2107 study, grade 3-4 bleeding was seen in 2.5% of the patients in chemotherapy-alone group and in 3.1% in the bevacizumab group; the rates were similar but 3 patients with grade 4 bleeding were in the bevacizumab group [3]. Saltz et al. reported that using concurrent anticoagulant therapy doesn't increase bleeding risk [9]. In the BEAT study [18] it was suggested that severe bleeding can be a sign for GIP. Bevacizumab increases the risk of bleeding, but grade 3-4 bleeding risk was found to be similar with placebo.

Grade 1-2 proteinuria was found in 8% of the patients; no grade 3-4 proteinuria was detected. The incidence of any grade of proteinuria was 38% in the AVF2192 trial [7], but in the BEAT study it was 10% [18]. In many studies grade 3 proteinuria was seen in

Table 4. Randomized studies including bevacizumab-containing regimens in the first-line treatment of metastatic colorectal cancer

Author, year, phase	*Treatment regimens including B (N)*	*Bevacizumab dose (mg/kg)*	*Any grade 3-4 toxicity (%)*	*AE causing discontinuation of therapy (%)*	*AE leading to death (%)*	*Mortality in 60 days (%)*	*Hypertension grade 3-4 (%)*	*Bleeding grade 3-4 (%)*	*GI perforation (%)*	*Proteinuria grade 3-4 (%)*	*Thrombotic event (any) (%)*	*Wound complications grade 3-4 (%)*
Kabbinavar, 2003, phase II (AVF0780) [6]	5-FU/LV+B (35) 5-FU/LV+B (33)	5 10	74 78	11 19	NR	NR	8.6 25.0	0 9.4	NR	NR	25.7 13	NR
Hurvitz, 2004, phase III (AVF2107) [3]	IFL+B (393)	5	84.9	8.4	2.6	3.00	11	3.1	1.5	<1	19.4	NR
Kabbinavar, 2005, phase II (AVF2192) [7]	5-FU/LV+B (100)	5	87	10	4	5	16	5	2	1	18	NR
Fuchs, 2007, phase III [8]	FOLFIRI+B (56) mIFL+B (59)	5 7.5	NR	16.1 13.6	NR	1.8 6.8	12.5 1.7	NR	NR	NR	NR	NR
Hockster, 2008, phase III [10]	mFOLFOX6+B (71) bFOL+B (70) XELOX+B (72)	5 5 7.5	59 51 56	NR	0 4 4	NR	6.1	NR	2.3	<1	NR	1.4
Tol, 2009, phase III [11]	XELOX+B (378) XELOX+B+Cetux (377)	7.5 7.5	73.2 81.7	NR	NR	1.9 2.7	14.8 9.3	1.6 0.5	0.3 1.6	NR	NR	NR
Sobrero, 2009, phase IV [12]	FOLFIRI+B (209)	5	NR	24	6	2	5	4	2	2	22	<1
Tebbutt, 2010, phase III [13]	C+B (157) CM+B (158)	7.5	NR	9 9	4.4 1.8	6 3	3.8 6.3	1.3 5.1	1.9 0.6	3.2 6.3	12.1 14.4	NR
Masi, 2010, phase II [14]	FOLFOXIRI+B (57)	5	NR	13	0	NR	11	0	NR	NR	7	NR
Saltz, 2011, phase, III [15]	mFOLFOX6+B (124) mFOLFOX6+B+Cetux (123)	5 5	NR	33.1 20.3	NR	4 1	4.2 0.8	NR	NR	NR	NR	NR

B: bevacizumab, IFL: irinotecan+bolus 5-FU+leucovorin, mIFL: modified IFL, mFOLFOX6: modified FOLFOX6, FOLFOXIRI: FOLFOX+irinotecan, XELOX: capecitabine+oxaliplatin, C: capecitabine, M: mitomycin, Cetux: cetuximab, LV: leucovorin, AE: adverse event, GI: gastrointestinal, NR: not reported

less than 2%, however, grade 4 proteinuria and nephrotic syndrome were not reported [3,7,10,12]. It is suggested that proteinuria is associated with glomerular capillary endothelial injury associated with the anti-VEGF effect and thrombotic microangiopathy [19]. Although the risk of renal injury is low, patients receiving bevacizumab should be monitored for urine protein once every 2-8 weeks; if proteinuria of ≥ 2 g/day occurs therapy must be interrupted and therapy must be stopped if nephrotic syndrome occurs.

The risk for thromboembolism is increased in MCRC patients because of cancer, surgical procedures and cytotoxic chemotherapy. The incidence of thromboembolic events were distinctively higher in patients who received bevacizumab in the AVF0780 trial (9% in the chemotherapy-alone group, 26% in the 5 mg/kg bevacizumab group, 13% in the 10 mg/kg bevacizumab group) [6]. In the AVF2107 and AVF2192 studies the thromboembolic event rates were relatively low (19.4% and 18%, respectively), when compared to AVF0780 [3,7]. On the other hand, ATE incidence was 2-fold higher in the bevacizumab group than in the chemotherapy-alone group in the AVF2192 trial, pointing to the need for more studies regarding this matter [7]. Although many studies found no increase in the risk of venous thromboembolism, ATE incidence was higher with bevacizumab therapy. A meta analysis which included 5 randomised controlled studies with 1745 patients in total, done by Scappaticci et al, found that the incidence of ATE was 2-fold higher in bevacizumab-receiving patients; age above 65 years and known ATE history were independent risk factors for ATE [20]. Similar results were reported in the BRITE study [5]. The risk of mortality from ATE is much lower than the survival advantage gained with bevacizumab usage, therefore the 2 risk factors which have been mentioned above are not contraindications for bevacizumab use. Scappaticci et al. mentioned that low dose acetylsalicylic acid could decrease the incidence of ATE associated with bevacizumab without increasing the risk of bleeding [20]. Furthermore, it is reported that bevacizumab-containing chemotherapy which is concurrently given with anticoagulant therapy is safe [21]. Many authors recommend that patients with ATE during bevacizumab treatment to discontinue treatment permanently [22,23]. In our study no arterial thromboembolism was seen, and venous thromboembolic events were seen in 3 patients; all of them were treated successfully with anticoagulant therapy and no recurrent thromboembolism was observed, but bevacizumab was stopped in all 3 patients permanently.

We observed GIP in 3 patients who applied to the emergency department with abdominal pain and vomiting, and diarrhea in 1 patient and constipation in 2. Two patients presented to hospital within 24 hours after the first symptom and were operated on successfully, but 1 patient who applied after 24 hours died because of septic shock. Bevacizumab was stopped permanently in 1 of these 2 patients; in the other one bevacizumab was re-administered without complications. GIP is one of the most life-threatening and specific complications of bevacizumab. Its incidence is 1- 4% [3,7,10-13]. Although the exact mechanism is not known, it is proposed that it occurs because of tumor necrosis in the bowel serosa which is associated with decrease in tumor angiogenesis and its blood supply [24]. Intraabdominal inflammation, gastrointestinal instrumentation like colonoscopy, abdominal/pelvic irradiation, unresected primary tumor, and peritoneal carcinomatosis are possible risk factors which increase predisposition to GIP [25]. Acetylsalicylic acid, nonsteroidal anti-inflammatory drugs and anticoagulant therapy are other possible risk factors [22]. The reported locations of perforation have included the stomach, and the small and large bowel. Abdominal pain, vomiting and constipation are the most typical symptoms [22,24,25]. In the BEAT study, 7 cases of all 38 treatment-related deaths were confirmed as a result of GIP [18]. GIP was registered in 2 patients in AVF2192 study; the first case was registered on the 110th day of therapy, and the other one on the 338th day [7]. In contrast, in the BRITE study GIP was detected in the early phases of therapy in most patients (median time to occurrence 2.4 months) [5]. In the AVF2107 study, 1 of 6 patients with GIP died, and the remaining 5 were treated successfully [3]. Partial or complete response had been achieved in all these 6 patients. Bevacizumab could be readministered after recovery in 3 of the 5 patients; however, many authors recommend to discontinue treatment permanently. In our study, the primary tumor had been resected in 2 of the 3 patients with GIP, and perforation happened after the 4th month of therapy in all 3 of them. We suggest that GIP should be taken into consideration in patients who apply with abdominal pain, vomiting and changing bowel habits. These patients should be hospitalized and investigated thoroughly. Early surgical intervention may be life-saving in these patients.

The negative effects of bevacizumab on wound healing are well known. Angiogenesis has a key role on wound healing, therefore it is expected that bevacizumab complicates the wound healing process through its anti-VEGF effect. This entity is especially important in patients receiving bevacizumab before or after a major surgical operation. Wound healing failure, delayed wound healing, wound dehiscence, bleeding, infection, abscess and/or fistula formation can occur in these patients [22,26]. Wound complication (WC) rates are less than 2% in various clinical trials [10,12,26]. In the

BRITE study which included 603 operated MCRC patients, serious WC rate was 4.5% [27]. Wound healing complications (WHC) occurred in 3 (5%) patients in our study. Predisposing factors for WC are infection or tumor involvement at the operation site, uncontrolled diabetes mellitus, and obesity [17,26]. Scappaticci et al. assessed the WC in patients who had undergone colorectal cancer surgery 28-60 days before bevacizumab-containing treatment and in those with major colorectal cancer surgery during bevacizumab-containing treatment; in the first group WC rate was 1.3%, and the second 13% (p=0.28) [26]. Although serious WC do occur in patients during bevacizumab treatment, whether therapy should be discontinued permanently is still controversial. Current literature suggests patients should wait for at least 6-8 weeks after cessation of bevacizumab treatment to have surgery [28,29]. In addition, postoperative reinitiation of bevacizumab must wait ≥28 days to prevent an increased risk of WC [29]. In our study 3 patients developed grade 1-2 WC and in all 3 patients WC occurred at the venous port access area. The treatment was interrupted for 2 weeks and after wound stabilisation bevacizumab treatment was reinitiated; wound site complications were not observed again. In a study, the incidence of severe central venous port complications requiring port change in patients who received bevacizumab was 3.1% [30]. It was also reported that patients who received bevacizumab in the first 10 days after port implantation had a higher risk of wound dehiscence [30]. As implantable venous access devices are widely used, there is a need for more studies about port complications in bevacizumab-receiving patients.

In conclusion, adverse events associated with bevacizumab in combination with chemotherapy are generally predictable and manageable. Bleeding and hypertension were the most commonly seen adverse events associated with bevacizumab in our study. Most of the events were grade 1-2. Thromboembolic events and GIP are the most common causes of therapy interruption. Our results are compatible with the relevant literature. In our study no ATE was seen; venous thromboembolic events were treated with standard treatment and did not recur, but resulted in permanent discontinuation of bevacizumab therapy. GIP was associated with one death in our study. Further studies about bevacizumab-related toxicities and their mechanisms will enable the prevention of these adverse events which cause therapy interruption and carry a substantial risk of morbidity and mortality.

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