Bevacizumab and Postoperative Wound Complications in Patients with Liver Metastases of Colorectal Cancer

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Abstract. *Aim: The present study investigated whether bevacizumab (BV) is associated with postoperative wound complications (PWCs). Patients and Methods: We retrospectively analyzed patients undergoing surgery for liver metastases of colorectal cancer at our Institution. Patients were divided into 3 groups according to the preoperative treatment: chemotherapy with BV (group A), chemotherapy without BV (group B) and no chemotherapy (group C). Results: Between February 2003 and September 2012, 297 patients underwent 373 surgeries. Groups A, B and C consisted of 23, 62 and 288 patients, respectively. PWCs occurred in 29 patients (7.8%). In multivariate analysis, there were no differences in PWCs among the groups (C vs. B:P=0.739; C vs. A: P=0.110). Conversely, lower serum albumin levels (<3.5g/dl vs. ≥3.5g/dl: p=0.030) and synchronous colorectal resection (no vs. yes; p<0.001) remained significant risk factors of developing PWCs. Conclusion: Chemotherapy with or without BV did not influence the risk of PWCs.*

Bevacizumab (BV), a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is an important component of colorectal cancer (1-4), non-small-cell lung cancer (5) and cervical cancer treatment (6). However, BV is associated with several major complications, such as hypertension, proteinuria, bleeding, thrombotic events and gastrointestinal perforation. It is also known to inhibit wound healing. Because the neovascularization process that supports tumor growth may be similar to that of normal wound repair, the use of anti-angiogenic agents, such as BV, in the surgical setting might impair or delay wound healing (7). The recommended interval between the last dose of BV and surgery is usually 6-8 weeks, which is decided on the basis of pharmacokinetics data (2 half-lives of BV) (8). Several retrospective series have addressed the safety of hepatectomy in patients who were administered BV prior to resection, none of which suggested that excess postoperative wound complications (PWCs) occur (9-17). However, available data that correlate the incidence of PWCs and the time since the last BV dose are conflicting.

Therefore, the present study investigated whether BV is associated with PWCs and clarified the appropriate interval between the last dose of BV and surgery in terms of clinical outcomes. Another aim of this study was to clarify other factors associated with PWCs in patients undergoing surgery for colorectal liver metastases.

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Key Words: Bevacizumab, postoperative wound complications, liver metastases of colorectal cancer.

Patients and Methods

We retrospectively analyzed patients who underwent surgery for liver metastases of colorectal cancer at our Institution between February 2003 and September 2012. Patients were divided into 3 groups according to the preoperative treatment administered within 24 weeks before surgery as follows: chemotherapy (CT×) with BV (group A), CT× without BV (group B), and no CT× (group C).

Data on patients' characteristics and operative factors were collected. Patients' characteristics included age, gender, the presence of diabetes mellitus, preoperative serum albumin levels, preoperative indocyanine green (ICG) 15-min retention rates, preoperative portal vein embolization and previous hepatic resection. Operative factors included the surgical procedure (partial hepatectomy or others, including segmentectomy, hemihepatectomy and extended hepatectomy), synchronous colorectal resection, the duration of surgery, estimated blood loss, intraoperative red blood cell (RBC) transfusion, the size of the largest hepatic metastasis, the number of hepatic metastases, surgical margins, postoperative complications associated with hepatectomy (bile leakage and intra-abdominal infection/abscess) and the

Table I. *Clinical variables*.

Variable	Group A CT× with BV (*n*=23) No.	(%)	Group B CT× without BV (*n*=62) No.	(%)	Group C No CT× (*n*=288) No.	(%)	*P*-Value
Age, years-median (range)	64 (48-76)		59 (35-77)		63 (22-86)		0.665
<65	13	(56.5)	39	(62.9)	162	(56.3)	
≥65	10	(43.5)	23	(37.1)	126	(43.8)	
Gender							0.061
Female	12	(52.2)	17	(27.4)	118	(41.0)	
Male	11	(47.8)	45	(72.6)	170	(59.0)	
Diabetes mellitus							0.828
No	21	(91.3)	53	(85.5)	245	(85.1)	
Yes	2	(8.7)	9	(14.5)	43	(14.9)	
Preoperative serum albumin, g/dl-median (range)	4.3 (3.1-4.7)		4.1 (3.3-4.9)		4.1 (2.6-5.1)		0.829
<3.5 g/dl	1	(4.3)	2	(3.2)	17	(5.9)	
≥3.5 g/dl	22	(95.7)	60	(96.8)	271	(94.1)	
Preoperative ICG 15-min retention rate, %-median (range)	11.3 (3.5-25.7)		8.0 (0.8-23.5)		7.3 (0.5-23.9)		0.058
<10%	10	(45.5)	34	(60.7)	154	(69.1)	
≥10%	12	(54.5)	22	(39.3)	69	(30.9)	
Preoperative portal vein embolization							0.009
No	21	(91.3)	53	(85.5)	276	(95.8)	
Yes	2	(8.7)	9	(14.5)	12	(4.2)	
Previous hepatic resection							0.209
No	17	(73.9)	53	(85.5)	217	(75.3)	
Yes	6	(26.1)	9	(14.5)	71	(24.7)	
Hepatic resection							0.008
Partial hepatectomy	14	(60.9)	30	(49.2)	201	(70.3)	
Segmentectomy, hemihepatectomy, and extended hepatectomy	9	(39.1)	31	(50.8)	85	(29.7)	
Synchronous colorectal resection							<0.001
No	22	(95.7)	57	(91.9)	204	(70.8)	
Yes	1	(4.3)	5	(8.1)	84	(29.2)	
Duration of surgery, min-median (range)	298 (126-702)		329 (53-790)		280 (71-680)		0.026
<300 min	12	(52.2)	25	(40.3)	170	(59.0)	
≥300 min	11	(47.8)	37	(59.7)	118	(41.0)	
Estimated blood loss, ml-median (range)	509 (62-1560)		780 (3-3400)		431 (4-3003)		<0.001
<500 ml	11	(47.8)	17	(27.4)	167	(58.0)	
≥500 ml	12	(52.2)	45	(72.6)	121	(42.0)	
Intraoperative RBC transfusion							0.775
No	23	(100)	59	(95.2)	277	(96.2)	
Yes	0	(0.0)	3	(4.8)	11	(3.8)	
Size of largest hepatic metastasis, cm-median (range)	2.5 (0.5-10.0)		3.3 (1.0-12.5)		2.7 (0.6-16.0)		0.076
≤3 cm	12	(57.1)	22	(37.9)	148	(53.8)	
>3 cm	9	(42.9)	36	(62.1)	127	(46.2)	
Number of hepatic metastases-median (range)	2 (1-13)		3 (1-10)		1 (1-25)		<0.001
1	7	(33.3)	19	(31.1)	162	(57.7)	
≥2	14	(66.7)	42	(68.9)	119	(42.3)	

Table I. *Continued*

Table I. *Continued*

Variable	Group A CT× with BV (*n*=23) No.	(%)	Group B CT× without BV (*n*=62) No.	(%)	Group C No CT× (*n*=288) No.	(%)	*P*-Value
Positive surgical margin							0.008
No	20	(95.2)	45	(75.0)	248	(89.5)	
Yes	1	(4.8)	15	(25.0)	29	(10.5)	
Postoperative hepatic complication							0.740
No	18	(78.3)	51	(82.3)	240	(83.3)	
Yes	5	(21.7)	11	(17.7)	48	(16.7)	
Bile leakage	5	(21.7)	10	(16.1)	44	(15.3)	
Intra-abdominal infection/abscess	1	(4.3)	2	(3.2)	8	(2.8)	
Length of hospital stay, days-median (range)	15 (9-33)		13 (9-35)		14 (5-49)		
Number of preoperative treatment regimens-median (range)	1 (1-4)		1 (1-4)		--		
Last-line regimen							
Oxaliplatin-based	14	(60.9)	11	(17.7)	--		
Irinotecan-based	3	(13.0)	10	(16.1)	--		
Other	6	(26.0)	41	(66.1)	--		
Duration of CT×, weeks-median (range)	25.3 (0.1-98.7)		28.4 (0.9-184.3)		--		
Time between the last dose of CT× and surgery, weeks-median (range)	9.7 (2.7-23.1)		9.2 (2.1-23.9)		--		
Duration of BV, weeks-median (range)	16.3 (0.1-94.4)		--		--		
Time between the last dose of BV and surgery, weeks-median (range)	10.4 (5.4-23.9)		--		--		
Total dose of BV, mg/kg-median (range)	35 (5-170)		--		--		

CT×, Chemotherapy; BV, bevacizumab; ICG, indocyanine green; RBC, red blood cell.

length of hospital stay. For groups A and B, preoperative treatment information was collected, including the number of CT× regimens, last-line regimen, duration of CT× and time between the last dose of CT× and surgery. For group A, the duration of BV use, time between the last administration of BV and surgery and total dose of BV were also determined. PWCs were defined to include wound infection, wound dehiscence, postoperative hemorrhage, hematoma and other wound complications according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (grade 1 or greater).

Univariate and multivariate logistic-regression analyses were performed to identify factors that were associated with the risk of PWCs. All point estimates, 95% confidence intervals (CIs) and *P*-values were calculated on the basis of the exact distributions of sufficient statistics. Contingency table analyses were performed to estimate and compare the proportion of patients with PWCs in each group. The Fisher's exact test was used to evaluate differences in patients' characteristics between the groups. The Wilcoxon rank-sum test was performed to assess between-group differences in the time between the last dose of BV and surgery and that between the last dose of CT× and surgery. All *P*-values were 2-sided. *P*-values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using the SAS software (version 9.3, SAS Institute, Inc., Cary, NC, USA). The logistic regression models were performed with the LOGISTIC procedure. The Wilcoxon rank-sum test and Fisher's exact test were performed with the NPAR1WAY procedure and FREQ procedure, respectively.

Results

Between February 2003 and September 2012, 297 patients underwent 373 surgeries for liver metastases of colorectal cancer (total of 373 patients). Twenty-three patients received CT× with BV (group A), 62 patients received CT× without BV (group B) and 288 patients received no CT× (group C) before surgery.

Patient's characteristics and operative factors are listed in Table I. Age, gender, the presence of diabetes mellitus, preoperative serum albumin levels, preoperative ICG 15-min

Table II. *Difference in the frequency of postoperative wound complications among the 3 groups.*

	Group A		Group B		Group C	
	CT× with BV (*n*=23)		CT× without BV (*n*=62)		No CT× (*n*=288)	
	No.	(%)	No.	(%)	No.	(%)
PWCs						
No	20	(87.0)	59	(95.2)	265	(92.0)
Yes	3	(13.0)	3	(4.8)	23	(8.0)
Wound infection	2	(8.7)	2	(3.2)	17	(5.9)
Wound dehiscence	0	(0.0)	1	(1.6)	4	(1.4)
Hematoma	0	(0.0)	0	(0.0)	2	(0.7)
Other	1	(4.3)	0	(0.0)	0	(0.0)

PWCs occurred in 29 patients (7.8%): wound infection, 21 patients; wound dehiscence, 5 patients; hematoma, 2 patients; and other, 1 patient (skin flap necrosis). CT×, Chemotherapy; BV, bevacizumab; PWCs, postoperative wound complications.

retention rates, previous hepatic resection rates, intraoperative RBC transfusion use, the size of the largest hepatic metastasis and postoperative hepatic complications (bile leakage and intra-abdominal infection/abscess) were similar among the 3 groups. Patients in group C were less likely to undergo preoperative portal vein embolization (4.2%), commonly underwent partial hepatectomy (70.3%) and synchronous colorectal resection (29.2%), tended to have a shorter duration of surgery and lower estimated blood loss and had smaller numbers of hepatic metastases than those in groups A and B. Patients in group B were more likely to have positive surgical margins (25.0%). The median number of preoperative CT× regimens was 1 (range=1-4) in groups A and B. Oxaliplatin-based regimens were most commonly used in group A. The median durations of CT× were 25.3 weeks (range=0.1-98.7 weeks) in group A and 28.4 weeks (range=0.9-184.3 weeks) in group B. The median times between the last dose of CT× and surgery were 9.7 weeks (range=2.7-23.1 weeks) in group A and 9.2 weeks (range=2.1-23.9 weeks) in group B. The median duration of BV was 16.3 weeks (range=0.1-94.4 weeks), the median time between the last dose of BV and surgery was 10.4 weeks (range=5.4-23.9 weeks) and the median total dose of BV was 35mg/kg (range=5-170mg/kg) in group A.

PWCs occurred in 29 patients (7.8%) as follows: wound infection, 21 patients; wound dehiscence, 5 patients; hematoma, 2 patients; other, 1 patient (skin flap necrosis). PWCs occurred in 3 patients (13.0%) in group A, 3 patients (4.8%) in group B and 23 patients (8.0%) in group C (Table II). There were no differences in the incidence of PWCs among the groups in both univariate (group C *vs*. group B: odds ratio [OR]=0.587; 95% CI=0.109-2.040; p=0.579; group C *vs*. group A: OR=1.725; 95% CI=0.306-6.497; p=0.599) and multivariate analyses (group C *vs*. B: OR=1.586; 95% CI=0.255-7.097; p=0.739; group C *vs*. group A; OR=4.619; 95% CI=0.712-22.339; p=0.110) (Table III). In univariate analysis, only 4 clinical variables were associated with the incidence of PWCs. Among them, lower preoperative serum albumin levels (<3.5g/dl) and synchronous colorectal resection appeared to be clinically important. In multivariate analysis, lower preoperative serum albumin levels and synchronous colorectal resection remained significant risk factors for the development of PWCs (preoperative serum albumin: <3.5g/dl *vs*. ≥3.5g/dl; OR=0.196; 95% CI=0.050-0.862; p=0.030; synchronous colorectal resection: no *vs*. yes; OR=5.579; 95% CI=2.027-16.838; p<0.001) (Table III).

We then compared PWCs according to the time between the last dose of BV and surgery for group A patients and that between the last dose of CT× and surgery for group B patients. We analyzed the risk of PWCs when the interval between the last dose of BV or CT× and surgery was less than 6, 7, 8, 9, 10, 11 and 12 weeks (Tables IV-V). The dose of BV did not significantly increase the frequency of PWCs when treatment was discontinued at least 6 weeks before surgery in univariate analysis. However, the risk of PWCs was greatest when BV was administered less than 7 weeks before surgery, (OR=9.664; 95% CI=0.395-706.231; p=0.215) and PWCs tended to decline in frequency as the time between the last dose of BV and surgery increased (Table IV). The dose of CT× also did not significantly increase the frequency of PWCs when discontinued at least 6 weeks before surgery in univariate analysis. However, PWCs tended to decrease in frequency as the time between the last dose of CT× and surgery increased (Table V).

Discussion

Our study suggested that the administration of preoperative BV did not influence the risk of PWCs. Several previous studies evaluated the influence of preoperative BV on surgical outcomes. Scappaticci *et al*. (9) assessed postoperative wound healing complications in 2 randomized trials of BV in the treatment of colorectal cancer. Wound healing complications were more frequent in patients who underwent major surgery during BV therapy, but this difference did not reach statistical significance. In the data reported by Reddy *et al*. (10), there were no differences in postoperative complications between patients given preoperative CT× with and without BV. Postoperative complications were more common when resection was performed within 8 weeks after the last BV administration, but this difference was not statistically significant. Kesmodel *et al*. (11) suggested that neither the use of BV nor the timing of BV administration (≤60 days *vs*. >60 days before surgery) was associated with an increase in postoperative complication rates. Okines *et al*. (12), D'Angelica *et al*. (13), Tamandl *et al*. (14), Wicherts *et al*. (15) and Van del Pool *et al*. (16) also reported that the addition of BV to standard CT× before the resection of colorectal liver metastases did not appear to increase

Table III. *Univariate and multivariate logistic-regression analyses of postoperative wound complications.*

Variables	Univariate analysis (*n*=373)		*p*-Value	Multivariate analysis (*n*=373)		*p*-Value
	Odds ratio	(95% CI)		Odds ratio	(95% CI)	
Group						
C: No CT×	1					
B: CT× without BV (C *vs*. B)	0.587	(0.109-2.040)	0.579	1.586	(0.255-7.097)	0.739
A: CT× with BV (C *vs*. A)	1.725	(0.306-6.497)	0.599	4.619	(0.712-22.339)	0.110
Preoperative serum albumin, g/dl						
<3.5 g/dl	1					
≥3.5 g/dl	0.220	(0.068-0.841)	0.027	0.196	(0.050-0.862)	0.030
Previous hepatic resection						
No	1					
Yes	0.230	(0.026-0.948)	0.039	0.532	(0.054-2.671)	0.670
Synchronous colorectal resection						
No	1					
Yes	6.142	(2.613-15.088)	<0.001	5.579	(2.027-16.838)	<0.001
Estimated blood loss, ml						
<500 ml	1					
≥500 ml	0.391	(0.146-0.949)	0.036	0.370	(0.121-1.014)	0.054
Age, years						
<65	1					
≥65	0.946	(0.399-2.176)	1.000			
Gender						
Female	1					
Male	1.070	(0.462-2.589)	1.000			
Diabetes mellitus						
No	1					
Yes	1.253	(0.357-3.571)	0.826			
Preoperative ICG 15-min retention rate, %						
<10%	1					
≥10%	1.569	(0.618-3.889)	0.389			
Preoperative portal vein embolization						
No	1					
Yes	0.344	(<0.001-1.625)	0.293			
Hepatic resection						
Partial hepatectomy	1					
Segmentectomy, hemihepatectomy, and extended hepatectomy	0.736	(0.273-1.796)	0.621			
Duration of surgery, min						
<300 min	1					
≥300 min	1.851	(0.805-4.388)	0.163			
Intraoperative RBC transfusion						
No	1					
Yes	2.044	(0.212-9.931)	0.596			
Size of largest hepatic metastasis, cm						
≤3 cm	1					
>3 cm	1.552	(0.674-3.684)	0.350			
Number of hepatic metastases						
1	1					
≥2	0.634	(0.262-1.468)	0.337			
Positive surgical margin						
No	1					
Yes	0.232	(0.006-1.479)	0.191			
Postoperative hepatic complication						
No	1					
Yes	0.536	(0.101-1.836)	0.463			

CI, Confidence interval; CT×, chemotherapy; BV, bevacizumab; ICG, indocyanine green; RBC, red blood cell.

Table IV. *Sub-group analyses of postoperative wound complications (group A).*

	Univariate analysis (*n*=23)		
Time between the last dose of BV and surgery	Odds ratio	(95% CI)	*p*-Value
>6 weeks	1		
≤6 weeks	7.958	(0.081-783.154)	0.498
>7 weeks	1		
≤7 weeks	9.664	(0.395-706.231)	0.215
>8 weeks	1		
≤8 weeks	4.330	(0.191-294.490)	0.538
>9 weeks	1		
≤9 weeks	3.497	(0.156-235.617)	0.664
>10 weeks	1		
≤10 weeks	2.352	(0.106-157.094)	0.932
>11 weeks	1		
≤11 weeks	1.317	(0.059-88.362)	1.000
>12 weeks	1		
≤12 weeks	1.073	(0.048-72.497)	1.000

BV, Bevacizumab; CI, confidence interval.

Table V. *Sub-group analyses of postoperative wound complications (group B).*

	Univariate analysis (*n*=62)		
Time between the last dose of CT× and surgery	Odds ratio	(95% CI)	*p*-Value
>6 weeks	1		
≤6 weeks	4.433	(0.218-275.146)	0.482
>7 weeks	1		
≤7 weeks	3.072	(0.152-189.709)	0.709
>8 weeks	1		
≤8 weeks	2.677	(0.132-165.101)	0.804
>9 weeks	1		
≤9 weeks	2.187	(0.108-134.777)	0.951
>10 weeks	1		
≤10 weeks	1.365	(0.067-84.234)	1.000
>11 weeks	1		
≤11 weeks	1.025	(0.050-63.497)	1.000
>12 weeks	1		
≤12 weeks	0.748	(0.037-46.617)	1.000

CT×, Chemotherapy; CI, confidence interval.

postoperative wound morbidity. In a single-center, non-randomized phase II trial by Gruenberger *et al*. (17), BV was safety administered until 5 weeks before liver resection in patients with metastatic colorectal cancer without increasing the rate of wound healing complications. According to the BRiTE observational cohort study by Kozloff *et al*. (18), the incidence of serious wound complications in patients who had their last dose of BV less than 2 weeks, 2-4 weeks, 4-6 weeks, 6-8 weeks or ≥8 weeks before surgery was 10, 3, 3, 6 and 2%, respectively. As mentioned previously, our study also suggested that the preoperative administration of BV did not influence the risk of PWCs and, to the best of our knowledge, this is the first report from Asia to investigate whether BV is associated with PWCs. In addition, our study indicated that not only CT× with BV but also CT× without BV did not influence the risk of PWCs.

In sub-group analysis, the dose of BV did not significantly increase the frequency of PWCs when discontinued at least 6 weeks before surgery. The half-life of BV is relatively long. In pharmacokinetic studies, the mean half-life of BV was approximately 21 days, but the range varied from 11 to 50 days (8). Therefore, it has generally been recommended to wait 6-8 weeks after the last dose of BV before performing an elective hepatic resection, which represents 2 half-lives of BV. Our results supported previous findings. However, even a relatively low dose of BV (0.3 mg/kg) can lead to undetectable levels of free VEGF in the systemic circulation (8). With a typical clinical dose of BV in patients with colorectal cancer of 5 mg/kg every 2 weeks, a period of 2 half-lives would leave the equivalent of a dose of 1.25 mg/kg in the circulation, which greatly exceeds the level of BV that has been observed to remove free VEGF from the circulation (8). This suggests that VEGF inhibition after BV therapy may persist for more than 4 half-lives (84 days, 12 weeks) (19). However, most studies, including ours, suggested that an interval of 6-8 weeks between the last dose of BV and surgery appeared to be appropriate. Therefore, it is unclear whether circulating VEGF levels are the correct predictor of the biologic effects of a molecule that exerts its effects largely *via* paracrine mechanisms in the tumor microenvironment (20).

In multivariate analysis, lower preoperative serum albumin levels (<3.5g/dl) and synchronous colorectal resection were associated with an increased risk of developing PWCs. Kesmodel *et al*. (11) also reported that lower serum albumin levels and concomitant surgical procedures were associated with an increased risk of developing postoperative complications. In data reported by Tamandl *et al*. (14), increased age, low serum albumin levels, resection of more than 3 liver segments and synchronous bowel procedures requiring an anastomosis were associated with an increased postoperative morbidity rate in patients who received CT× (with or without BV) before hepatic surgery.

Our study has several limitations. First, this study was a retrospective analysis of a single institutional experience and, thus, definitive conclusions regarding whether BV influences the incidence of PWCs or what is the appropriate interval between the last dose of BV and surgery cannot be drawn. Second, although this study is one of the largest studies to investigate PWCs in patients with colorectal liver metastases, the number of patients who received CT× with BV before surgery was small. Third, we were unable to determine whether brief intervals between the last BV administration and surgery (such as 5

weeks, as reported by Gruenberger *et al*. (17)) were associated with PWCs because we used an interval of at least 5.4 weeks between the last dose of BV and surgery at our Institution.

In conclusion, this study suggested that the administration of preoperative CT× with or without BV did not influence the risk of PWCs. In sub-group analysis, the dose of BV did not significantly increase the frequency of PWCs when treatment was discontinued at least 6 weeks before surgery. However, PWCs tended to decrease in frequency as the time between the last administration of BV and surgery increased. In multivariate analysis, lower serum albumin levels (<3.5g/dl) and synchronous colorectal resection were associated with an increased risk of developing PWCs.

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