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Relationship Between Safety and Cumulative Bevacizumab Dose in Patients With Metastatic Colorectal Cancer Who Received Long-term Bevacizumab Treatment

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Abstract. *Background/Aim: Bevacizumab-based chemotherapy is the standard treatment for metastatic colorectal cancer (mCRC) but has several specific adverse events. The cumulative bevacizumab dose (CBD) increases with long-term treatment as it is often used beyond the first disease progression, based on existing evidence. However, the association between CBD and the frequency and severity of adverse events in mCRC patients who received bevacizumab for long-term treatment remains unclear. Patients and Methods: Among the mCRC patients who received bevacizumab-based chemotherapy between March 2007 and December 2017 at the University of Tsukuba Hospital, those who continued treatment for more than 2 years were eligible for the study. The onset and worsening of proteinuria, hypertension, bleeding, and thromboembolic events were assessed to determine their relationship with CBD. Results: Of the 109 patients who received bevacizumab-based chemotherapy, 24 were included in the study. Grade 3 proteinuria was observed in 21 (88%) and 9 (38%) patients. The severity of proteinuria markedly increased after administering >100 mg/kg of CBD and progressed to grade 3 at concentrations exceeding 200 mg/kg. Thromboembolic events were observed in three (13%) patients, and two of them developed acute myocardial infarction after receiving a CBD of >300 mg/kg. Grade 2 or higher hypertension and grade 1 bleeding were observed in 9 (38%) patients and in 6 (25%) patients, respectively, regardless of the CBD. Conclusion: Proteinuria and thromboembolic events occurred and worsened in mCRC patients when the bevacizumab dose exceeded the threshold dose.*

Colorectal cancer is the third leading cause of cancer-related deaths worldwide and the second leading cause of cancer-related deaths in Japan (1). For metastatic colorectal cancer (mCRC), bevacizumab, an angiogenesis inhibitor, is used as the standard treatment in fluoropyrimidine combination with oxaliplatin or irinotecan-based doublet chemotherapy, which is generally administered at 2.5 mg/kg/week (2). The median progression-free survival time with first-line chemotherapy, including bevacizumab, is 8-15 months (2-4). In addition, the significance of continuing bevacizumab treatment even after disease progression has been proven in a previous randomized phase III trial; bevacizumab is frequently used as a second-line treatment after failure of bevacizumab-based first-line therapies (5-7). Although the long-term administration of bevacizumab has shown a survival benefit, the increased incidence and severity of bevacizumab-related adverse events (AEs) remain a concern.

Bevacizumab-related AEs included proteinuria, hypertension, arterial or venous thrombosis, bleeding, gastrointestinal perforation, and delayed wound healing (2). Several studies have investigated the association between bevacizumab treatment duration and bevacizumab-related AEs. The severity of proteinuria and cardiovascular events increases with long-term use of bevacizumab (8). A similar relationship has been shown between the risk of proteinuria and cardiovascular events and trastuzumab for human epidermal growth factor receptor 2-positive breast cancer and rituximab for lymphoma, which are used for long-term treatment (9, 10).

However, another study reported that a high single dose of bevacizumab was correlated with the risk of developing

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proteinuria and hypertension, without considering the cumulative dose (11). The dose of bevacizumab varies by cancer type, such as 5 mg/kg/week for lung and breast cancers and 2.5 mg/kg/week for colorectal cancer; thus, it is difficult to associate the risk of developing AEs with the exposure duration or a single exposure dose.

Therefore, we hypothesized that the cumulative bevacizumab dose (CBD) would affect the risk of developing AEs. In this study, we aimed to evaluate the relationship between CBD and the incidence and severity of bevacizumab-related AEs in patients with mCRC who received long-term bevacizumab treatment.

Patients and Methods

Patients. Among the patients with mCRC who received bevacizumab-based chemotherapy between March 2007 and December 2017 at the University of Tsukuba Hospital, those who continued treatment for more than 2 years were eligible for the study. The cut-off date was August 2020. This study was approved by the Ethics Review Committee of our institution (R1-009).

Data collection. Data on patient's background, duration of bevacizumab treatment, CBD, time to onset of initial bevacizumab-related AEs, time to the worst grade of the corresponding AE, and reasons for discontinuation of bevacizumab were collected from the medical records.

Statistical analysis. The bevacizumab treatment duration was defined as the period from the initial dose to the date of the last dose. Patients who were treated with bevacizumab were assessed for proteinuria, hypertension, bleeding, cardiovascular events, gastrointestinal perforations, and delayed wound healing. The severity of AEs was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Since proteinuria was evaluated using the dipstick test, the scores of 2+ and 3+ were replaced with grade 2 and grade 3, respectively. Initial onset of AEs was defined as worsening of grade 1 or higher AEs. Continuous variables were expressed as medians and ranges, whereas categorical variables were expressed as numbers and proportions. The relationship between CBD and the onset of bevacizumab-related AEs was evaluated using the Kaplan–Meier method. IBM SPSS Statistics (version 21.0; SPSS Inc., Chicago, IL, USA) was used for performing statistical analysis.

Results

Patients. Among 109 patients who received bevacizumab-based chemotherapy between March 2007 and December 2017, 24 were treated with bevacizumab for more than 2 years (Table I). The median follow-up time was 58.5 months (range=35.3-121.4 months). The median age was 63 years (range=49-74 years), and 19 patients (79%) were men. Ten patients (42%) had an underlying hypertension, of whom five were treated with antihypertensive drugs (calcium antagonist in two patients and calcium antagonists plus angiotensin-converting enzyme or angiotensin receptor blocker in three patients). Twenty-three patients received an oxaliplatin-containing doublet regimen, while one patient received a triplet regimen (oxaliplatin, irinotecan, and fluoropyrimidine). The bevacizumab dose used in the biweekly regimen was 5.0 mg/kg on day 1 administered for 14 days, whereas that used in the triweekly regimen was 7.5 mg/kg on day 1 administered for 21 days. A bevacizumab dose of 2.5 mg/body/week was used, and dose reduction was not performed in all cycles. Twenty-three patients received oxaliplatin-containing therapy, of whom nine patients subsequently received irinotecan-containing therapy combined with bevacizumab. During the cut-off date, 13 patients continued to receive bevacizumab treatment, and the median duration of bevacizumab treatment was 39.1 months [95% confidence interval (CI)=32.3-45.9 months]. The median CBD dose was 323 mg/kg (range=80-945 mg/kg). The median relative dose intensity of bevacizumab was 0.98 (range=0.58-1.00). Eleven patients died, and the median OS was 75.4 months (95%CI=50.6-100.2).

Bevacizumab-related adverse events. The different bevacizumab-related AEs are listed in Table II. Grade 3 or higher proteinuria was observed in 21 (88%) and 9 (38%) patients, respectively. The grade 2 or higher hypertension was observed in nine (38%) patients, whereas grade 3 or higher hypertension was not observed in patients who received antihypertensive drugs prior to bevacizumab treatment. Grade 1 bleeding was reported in six patients (25%). Thromboembolic events were observed in three (13%) patients, whereas acute myocardial infarction occurred in two patients. Gastrointestinal perforation and delayed wound healing were not observed. Bevacizumab-related death was not reported.

The relationship between CBD and initial onset of related AEs is shown in Figure 1. Grade 1 or higher proteinuria tended to worsen when the dose exceeded 100 mg/kg (Figure 1A). The incidence rates of proteinuria before and after administering a CBD of 100 mg/kg were 14% and 86%, respectively. Hypertension and bleeding tended to worsen prior to the administration of a 100 mg/kg dose but were eventually controlled thereafter (Figure 1B and C). Pulmonary thromboembolism developed in one patient who received a CBD of 100 mg/kg, whereas acute myocardial infarction developed in two patients who received a CBD of >300 mg/kg (Figure 1D). Grade 3 proteinuria was associated with a CBD of >200 mg/kg (Figure 1A). In patients with grade 3 proteinuria, the median recovery time to grade 1 or lower was 28 days (range=14-238 days) after discontinuation of bevacizumab. Worsening of other AEs to grade 3 or higher were not associated with the CBD. Bevacizumab treatment was discontinued in 20 patients due to disease progression [16 patients (67%)], occurrence of acute myocardial infarction [2 patients (8%)], and achievement of complete response [2 patients (8%)].

Table I. *Demographic and baseline characteristics (n=24).*

Characteristic		n	%
Age, years	Median (range)	63 (49-74)	
Sex	Male	19	79
	Female	5	21
Body weight, kg (range)	Median (range)	60 (46.0-72.2)	
Body mass index	Median (range)	23 (20-27)	
ECOG performance status	0	19	79
	1	5	21
Pathologic type	Well or moderately differentiated Adenocarcinoma	23	96
	Unknown	1	4
KRAS/NRAS status	Wild	10	42
	Mutant	9	38
	Unknown	5	21
Primary tumour location	Right side (cecum, ascending, and transverse colons)	4	17
	Left side (descending and sigmoid colons and rectum)	20	83
Metastatic organ site	Liver	8	33
	Lung	7	29
	Lymph node	13	54
	Peritoneum	5	20
	Ovary	2	8
Comorbidity	Hypertension	10*	42
	Diabetes mellitus	2	8
Medical history	Old myocardial infarction	2	8
Cumulative dose of bevacizumab**	Median (range), mg/kg	323 (80-945)	
Cytotoxic agents in combination with bevacizumab	FOLFOX/CAPOX/SOX	14	58
	FOLFOX/CAPOX/SOX to FOLFIRI/IRIS	9	38
	FOLFOXIRI	1	4

FOLFOX: Infusional 5-fluorouracil/leucovorin + oxaliplatin; CAPOX: capecitabine + oxaliplatin; SOX, S-1 + oxaliplatin; FOLFIRI: infusional 5-fluorouracil/leucovorin + irinotecan; IRIS: S-1 + irinotecan; FOLFOXIRI, infusional 5-fluorouracil/leucovorin + oxaliplatin + irinotecan; ECOG: Eastern Cooperative Oncology Group. *Grade 2 and 3 adverse events occurred in 2 and 3 patients, respectively. **The dosage of bevacizumab used was 2.5 mg/kg/week in all patients.

Table II. *Bevacizumab-related adverse events.*

	Grade 1	Grade 2	Grade 3	Grade 4	Any (%)	Grade ≥3 (%)
Proteinuria*	8	4	9	–	21 (88)	9 (38)
Hypertension**	NE	5	4	0	9 (38)	4 (17)
Bleeding	6	0	0	0	6 (25)	0 (0)
Thromboembolic event	0	0	1	2	3 (13)	3 (13)
Gastrointestinal perforation	0	0	0	0	0	0
Delayed wound healing	0	0	0	0	0	0

*Dipstick test scores 2+ and 3+ are defined as grades 2 and 3, respectively. **The patients' hypertension as a comorbidity worsened to ≥grade 1, and patients who developed hypertension after bevacizumab treatment were counted. NE: Not evaluated.

Discussion

The present study showed a relationship between CBD and related AEs in patients with mCRC who received long-term bevacizumab treatment, with a median follow-up period of 58.5 months. In particular, proteinuria and thromboembolic events occurred when the bevacizumab dose exceeded the threshold dose.

The incidence of the initial onset of proteinuria clearly increased after administering a CBD of 100 mg/kg. Moreover, severe proteinuria developed as the CBD increased. The severe proteinuria developed when the CBD dose administered was >200 mg/kg (2 years after the administration period). Bevacizumab treatment for more than 1 year increases the incidence of severe proteinuria when the dose of bevacizumab for breast cancer is 5 mg/kg/week, corresponding to a

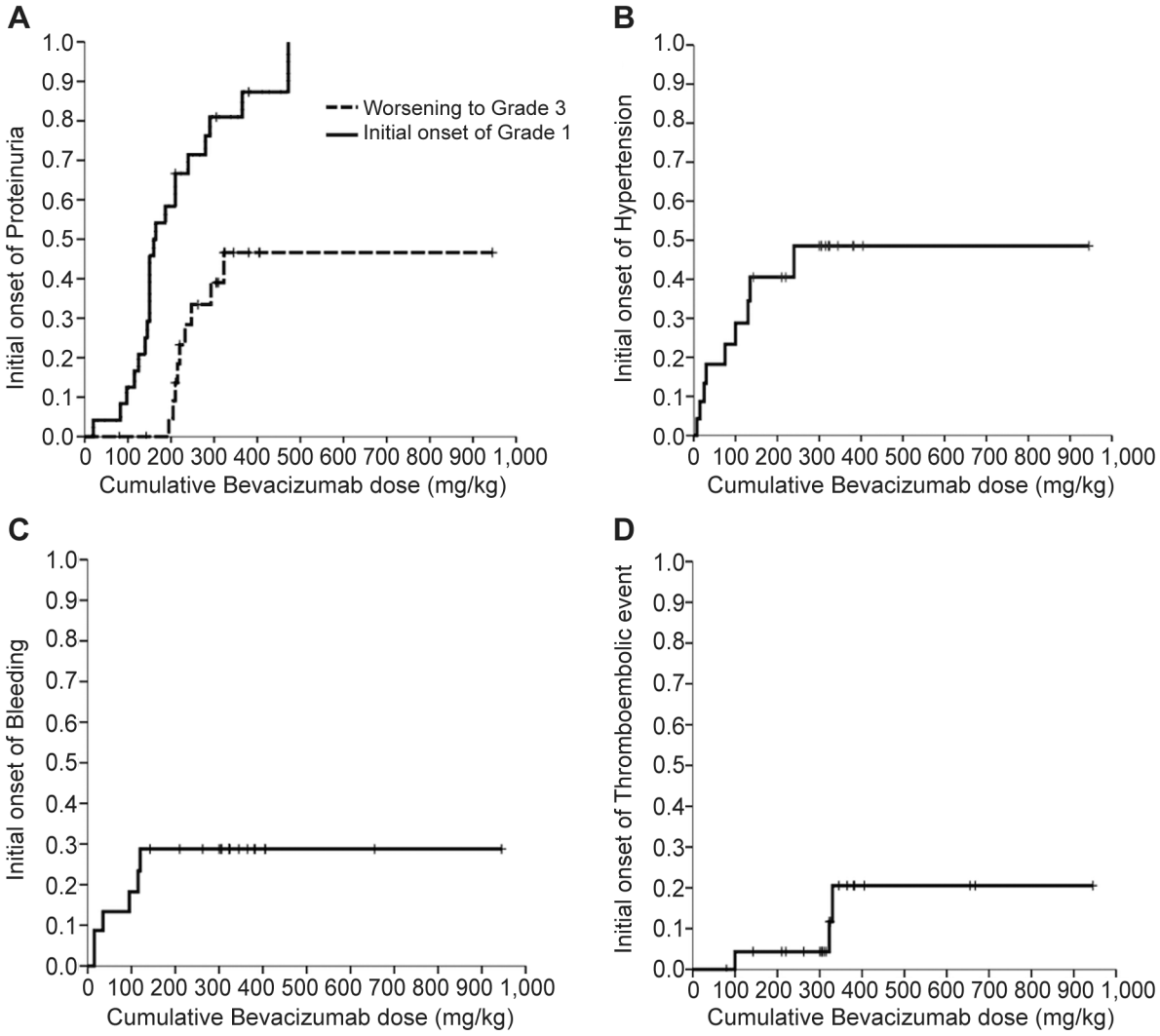

Figure 1. *Relationship between the cumulative bevacizumab dose and initial onset of bevacizumab-related adverse events. (A) Initial onset of ≥grade 1 to grade 3 proteinuria, (B) ≥grade 2 hypertension, (C) grade 1 bleeding, and (D) ≥grade 3 thromboembolic event.*

cumulative dose of approximately 200 mg/kg (12). The CBD for severe proteinuria in patients with breast cancer was comparable to that in patients with mCRC when bevacizumab was administered at 2.5 mg/kg/week. Therefore, the development of severe proteinuria was cumulative dose-dependent and not time-dependent. In our study, the severity of proteinuria decreased to grade 1 or less in all patients following the discontinuation of bevacizumab treatment. However, as the period of discontinuation of bevacizumab treatment was approximately 8 months in some patients, future studies should investigate the timing of bevacizumab discontinuation.

A high incidence of thromboembolic events was observed in three male patients (12.5%), particularly in two patients who developed acute myocardial infarction when the cumulative dose exceeded 300 mg/kg, corresponding to a period of 3 years. A previous meta-analysis of the association between bevacizumab and cardiovascular events showed that the risk ratio for myocardial ischemic heart disease increased to 1.75 in patients treated from 11 to 14 months, 4.02 in patients treated from 21 to 24 months, and 5.16 in patients treated >24 months compared with those who did not receive bevacizumab (8). This finding may support our results. On the contrary, long-term treatment with bevacizumab for breast cancer was not associated with severe arterial thromboembolic events or venous thromboembolic events, with 2.4% of these patients treated for 18 months or more and 1.0% for 24 months or more. A potential bias may exist as men are more likely to develop ischemic heart disease compared with women, especially Asians (13); however, attention should be paid to patients receiving higher CBD.

The incidence of bevacizumab-related bleeding and hypertension was poorly associated with CBD as their onset plateaued at a certain cumulative dose. A previous meta-analysis evaluating the risk of bevacizumab-related bleeding in patients with CRC showed that the risk of developing this condition within 6 months was higher than that after 6 months (14). No time-dependent increase was observed in the risk of bleeding in patients treated with bevacizumab compared with that in patients who received chemotherapy without bevacizumab (8). Hypertension commonly occurred shortly after the initiation of bevacizumab treatment (15). These findings and our results suggest that bleeding and hypertension are independent of CBD.

Our study has several limitations. This was a single-centre retrospective study with a small sample size. The severity of proteinuria was assessed based on urine protein dipstick test results. A previous report has shown that this method overestimates severe proteinuria compared to the urine protein-creatinine ratio, which was used as an alternative quantitative examination for proteinuria (16, 17). Although dipstick tests 2+ and 3+ were included in grade 2 proteinuria by CTCAE ver. 5.0, grade 1 proteinuria remained dipstick test grade 1+. The relationship between severe proteinuria and CBD should be re-evaluated; however, our results for the first onset of proteinuria are highly significant.

In conclusion, proteinuria and thromboembolic events develop in patients with mCRC who received long-term bevacizumab treatment when the bevacizumab dose exceeded the threshold dose.

Conflicts of Interest

None of the Authors have any conflicts of interest to disclose in relation to this study.

Authors' Contributions

S. Fukuda, Y. Niisato, M.T., S.F., Y.H., T.O., H.S., Y.T. collected clinical data. S.F., Y.N. and T.M. analyzed data. S.F. and T.M. wrote the manuscript. All Authors critically reviewed the manuscript and checked the final version.

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