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Risk factors increasing blood pressure in Japanese colorectal cancer patients treated with bevacizumab

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Bevacizumab has been reported to increase blood pressure. However, the factors, including patient characteristics and laboratory data contributing to this side effect remain unclear. Therefore, we investigated the relationships between increased blood pressure and bevacizumab administration, patient characteristics, and laboratory data. Between April 2007 and January 2018, factor analysis was retrospectively conducted by monitoring increases in blood pressure, the status of bevacizumab administration, patient characteristics, and laboratory data before the first administration in Japanese patients with colorectal cancer who satisfied the criteria for this study. Sixty-seven patients were included, 34 of whom (50.7%) had an increase in blood pressure after bevacizumab administration. On univariate analysis, liver metastasis, antihypertensive drug use, systolic blood pressure at rest before the first bevacizumab administration, body mass index, creatinine, and blood platelet count were significantly different between the two groups. Multivariate analysis was conducted using increased blood pressure as an objective variable and the factors extracted by the univariate analysis as explanatory variables. The results suggested that liver metastasis, antihypertensive drugs, systolic blood pressure at rest before the first bevacizumab administration, and creatinine were associated with the increase in blood pressure. Furthermore, a log-rank test performed based on Kaplan-Meier curves demonstrated that liver metastasis in patients not taking antihypertensive drugs and antihypertensive drug use in patients without liver metastasis were significantly associated with increased blood pressure. Additionally, liver metastasis in patients with antihypertensive drug use was significantly associated with increased blood pressure. Our findings suggest that liver metastasis and antihypertensive drug use, which was previously reported, are risk factors for increased blood pressure.

1. Introduction

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). VEGF is a cytokine that enhances vascular permeability and controls the cell division of vascular endothelial cells. Its expression is increased in several cancer cells. Bevacizumab inhibits the binding of VEGF to its receptor, which is expressed on vascular endothelial cells, by specifically interacting with VEGF. Bevacizumab suppresses angiogenesis in tumor tissues by preventing the biological activity of VEGF, which inhibits tumor growth. In addition, bevacizumab improves the accessibility of anticancer agents to tumors as a result of the decrease in interstitial pressure in tumor cells due to reduced vascular permeability via VEGF (AVASTIN Japanese interview form; Ferrara et al. 2003; Ferrara and Davis-Smyth 1997; Presta et al. 1997; Willett et al. 2004; Gerber and Ferrara 2005).

Bevacizumab is indicated for unresectable progressive or recurrent colon and rectal cancers, non-small-cell lung cancers, excluding squamous cell cancers, ovarian cancers, progressive or recurrent cervical cancers, inoperable or recurrent breast cancers, and malignant glioma. The main adverse reactions to bevacizumab are hypertension, proteinuria, and bleeding. Among these, hypertension is reported to occur in 18% of all patients treated. Therefore, blood pressure monitoring and control are important because several fatalities resulting from hypertensive encephalopathy or hypertensive crisis have been reported (AVASTIN Japanese package insert). The reported mechanisms of hypertension induced by bevacizumab are the suppression of endogenous nitric oxide synthesis in the vascular endothelium by VEGF inhibition (Ferrara et al. 2003), and reduction of the microvascular bed (Feihl 2006), which increases peripheral vascular resistance. In the clinical setting, some patients first exhibit an increase in blood pressure after bevacizumab administration and others redevelop increased blood pressure even under antihypertensive drugs. According to the Special Drug Use-Results Survey in Japan (AVASTIN Special drug use surveillance) and the report by Wicki et al. (2014), a past history or complication of hypertension, and antihypertensive drug use, respectively, were found to be risk factors for increased blood pressure by bevacizumab. Meta-analyses concluded that a single dose of bevacizumab and tumor type were risk factors for a marked increase in blood pressure (An et al. 2010).

However, few studies on risk factors for increased blood pressure by bevacizumab using patient characteristics and laboratory data have been reported. Therefore, the aim of this study was to evaluate factors related to increased blood pressure by evaluating bevacizumab administration, patient characteristics, and laboratory data in Japanese colorectal cancer patients.

2. Investigations and results

2.1. Patient characteristics and laboratory data

A total of 67 patients were included in the study, 34 of whom (50.7%) had an increase in blood pressure. The median frequency of bevacizumab administration was 3 times (range: 1-12), and the median cumulative dose of bevacizumab was 1,050 mg (range: 375-3,960) when the increase in blood pressure was noted. In the 34 patients with an increase in blood pressure, a single dose of bevacizumab

was 5 mg/kg in 27, 7.5 mg/kg in 6, and 10 mg/kg in 1. In the 33 patients without an increase in blood pressure, the doses were 5 mg/kg in 29 and 7.5 mg/kg in 4, demonstrating no significant difference between the two groups. The average systolic blood pressure (SBP) at rest before the first bevacizumab administration was significantly higher in patients with an increase in blood pressure than in patients without an increase in blood pressure (128.5±11.1 and 116.6±13.3 mmHg, respectively, p<0.05). There was no significant difference in diastolic blood pressure (DBP) at rest before the first bevacizumab administration between the two groups (71.3±10.6 and 71.1±10.4 mmHg, respectively). As shown in Table 1, among the patient characteristics, the presence of liver metastasis, antihypertensive drug use, and body mass index (BMI) were significantly different between the two groups (p<0.05). Regarding laboratory data, creatinine (CRE) and blood platelet count (PLT) were significantly different between the two groups (p<0.05), as shown in Table 2.

Table 1: Patient characteristics with and without an increase in blood pressure after bevacizumab administration

	Increased blood pressure (+)	Increased blood pressure (-)	p-value	
Age	69.7±9.3	66.5±11.5	0.21	*1
Sex (male/female)	24/10	19/14	0.20	*2
Height (cm)	159.3±9.2	161.3±9.6	0.39	*1
Body weight (kg)	58.3±11.7	54.3±11.5	0.16	*1
BMI (kg/m^2)	22.8±3.4	20.7±2.9	0.0065	*1
BSA (m^2)	1.55±0.18	1.52±0.20	0.45	*1
PS (ECOG) (0-1/2)	34/0	32/1	-	-
Previous chemotherapy (+/-)	32/2	30/3	0.49	*2
Stage of cancer (3/4)	4/30	9/24	0.097	*2
Liver metastasis (+/-)	23/11	12/21	0.0099	*2
Antihypertensive drugs (+/-)	19/15	7/26	0.0036	*2
Diabetes mellitus (+/-)	5/29	1/32	0.11	*2

Data are presented as the mean±standard deviation, n, or score. BMI, body mass index; BSA, body surface area; PS, performance status.
*1 : Student's t-test
*2 : Fisher's exact test

Table 2: Laboratory values with and without an increase in blood pressure after bevacizumab administration

	Increased blood pressure (+)	Increased blood pressure (-)	p-value	
WBC	5557±1777	6018±2185	0.35	*1
Neut	3458±1628	3807±2054	0.53	*2
Hb (g/dL)	12.0±1.7	12.1±1.9	0.81	*1
PLT (×10^4)	17.1±6.3	21.1±6.7	0.014	*1
T-Bil (mg/dL)	0.57±0.17	0.64±0.36	0.72	*2
AST (IU/L)	28.4±12.1	31.8±25.8	0.98	*2
ALT (IU/L)	22.4±13.9	21.9±11.9	0.71	*2
ALP (IU/L)	295.7±136.2	376.3±279.3	0.38	*2
CRE (mg/dL)	0.78±0.18	0.68±0.14	0.0090	*1
Ccr (mL/min)	ND	ND	-	-
Estimated Ccr (mL/min)	72.1±21.6	78.4±22.0	0.24	*1
Proteinuria (2+/+/±//unmeasured)	1/0/2/8/23	0/0/0/5/28	-	-
Alb (g/dL)	4.0±0.5	3.8±0.6	0.25	*1
LDH (IU/L)	225.5±94.0	350.9±478.5	0.32	*2

Data are presented as the mean±standard deviation or n. T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; CRE, creatinine; Ccr, creatinine clearance; Alb, albumin; LDH, lactate dehydrogenase; ND, not determined. HbA1c was measured only in 1 patient (HbA1c:5.9) with an increase in blood pressure, and in no patient without an increase in blood pressure.
*1 : Student's t-test
*2 : Mann-Whitney's U-test

2.2. Two-value logistic regression analysis

Multivariate analysis was conducted using the increase in blood pressure as an objective variable and the factors extracted by the univariate analysis as explanatory variables. As shown in Table 3, liver metastasis, antihypertensive drug use, SBP at rest before the first bevacizumab administration, and CRE were found to be associated with the increase in blood pressure (odds ratio: 9.69, 95% confidence interval: 2.01-46.74, p<0.05, odds ratio: 5.92, 95% confidence interval: 1.23-28.49, p<0.05, odds ratio: 1.06, 95% confidence interval: 1.00-1.12, p<0.05, odds ratio: 136.17, 95% confidence interval: 1.52-12186.25, p<0.05, respectively).

Table 3: Multivariate analysis (two-value logistic regression analysis)

	Odds ratio	95% confidence interval	p-value
Liver metastasis (+)	9.69	2.01 - 46.74	0.005
Antihypertensive drugs (+)	5.92	1.23 - 28.49	0.027
Systolic blood pressure	1.06	1.00 - 1.12	0.048
BMI	1.05	0.86 - 1.29	0.628
CRE	136.17	1.52 - 12186.25	0.032
PLT	0.96	0.86 - 1.06	0.434

BMI, body mass index; PLT, platelet count; CRE, creatinine.

2.3. The log-rank test with Kaplan-Meier curves for the increase in blood pressure

The log-rank test was performed based on Kaplan-Meier estimates of blood pressure increase, and liver metastasis in patients without antihypertensive drug use and antihypertensive drug use in patients without liver metastasis were demonstrated to be significantly associated with increased blood pressure (p<0.05) (Figs. 1 and 2). Additionally, liver metastasis in patients with antihypertensive drug use was significantly associated with increased blood pressure (p<0.05) (Fig. 3). Among patients without antihypertensive drug use, although 7 administrations of bevacizumab led to increased blood pressure in 50% of the patients with liver metastasis, the amount of bevacizumab administered in this study was not sufficient to increase blood pressure in 50% of the patients without liver metastasis (Fig. 1). Similarly, among patients without liver metastasis, six administrations of bevacizumab led to increased blood pressure in 50% of the patients on antihypertensive drugs, but the amount of bevacizumab administered in this study was not sufficient to increase blood pressure in 50% of the patients who

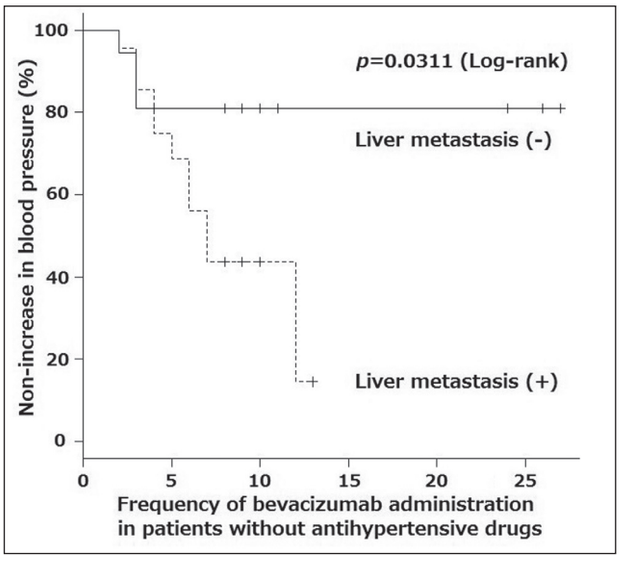

Fig. 1: Kaplan-Meier estimates of blood pressure increase with and without liver metastasis in patients without antihypertensive drugs

were not on antihypertensive drugs (Fig. 2). Furthermore, among patients using antihypertensive drugs, although three administrations of bevacizumab led to increased blood pressure in 50% of the patients with liver metastasis, six administrations of bevacizumab led to increased blood pressure in 50% of the patients without liver metastasis (Fig. 3). Of the 67 patients, 12 had both antihypertensive drug use and liver metastasis (17.9%), 23 only had liver metastasis (34.3%), 14 only had antihypertensive drug use (20.9%), and 18 had neither (26.9%).

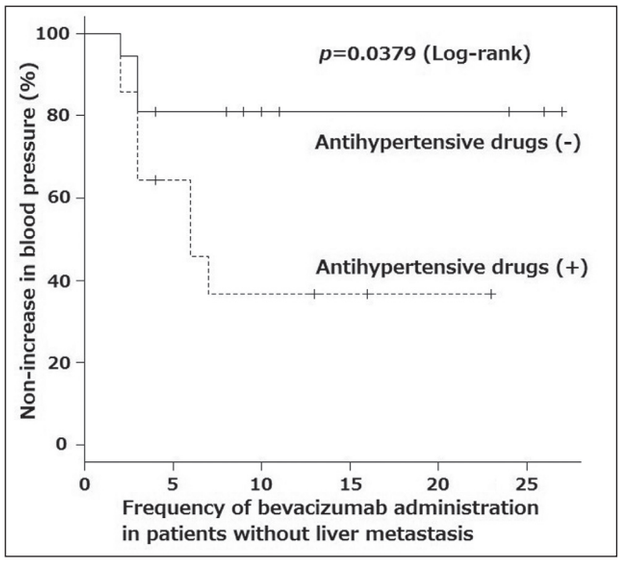

Fig. 2: Kaplan-Meier estimates of blood pressure increase with and without antihypertensive drug use in patients without liver metastasis

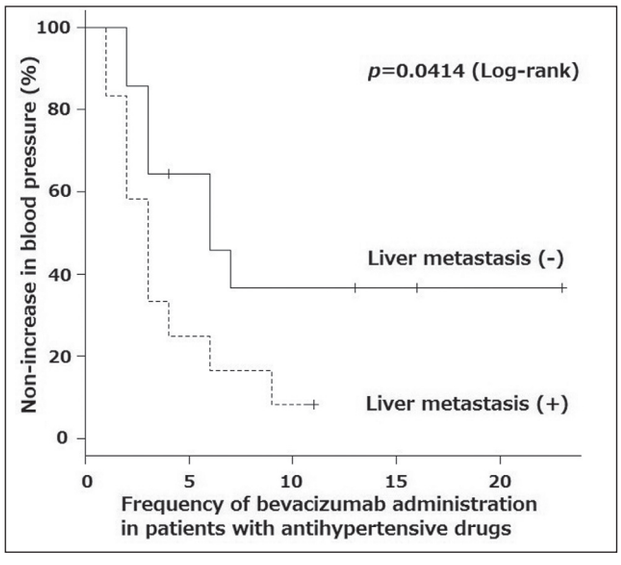

Fig. 3: Kaplan-Meier estimates of blood pressure increase with and without liver metastasis in patients with antihypertensive drugs

3. Discussion

This survey suggested that risk factors for increased blood pressure include liver metastasis in addition to the oral administration of antihypertensive drugs, which was previously reported. Bevacizumab is not metabolized via oxidation/reduction responses to drug-metabolizing enzymes. It may be captured by the reticuloendothelial system, such as in the liver and spleen, via Fc receptors or other *in vivo* receptors, leading to its disappearance from the circulation (Ghetie and Ward 2000). Therefore, in the presence of liver metastasis, decomposition by the reticuloendothelial system of the liver may have been affected, causing high bevacizumab concentrations to be maintained, resulting in enhanced activity. However, this cannot be concluded in the absence of reports on the pharmacokinetics of this drug in patients with liver metastasis. The frequency of liver metastasis was previously reported to be 70-87% in colorectal cancer patients treated with first-line chemotherapy (Dy et al. 2007; Tournigand et al. 2004; Okines et al. 2009; Douillard et al. 2010; Maughan et al. 2011). Therefore, careful follow-up is needed because the same frequency may be noted in colorectal cancer patients treated with bevacizumab.

According to this survey, the increase in blood pressure was 50.7%. However, a clinical trial and the Special Drug Use-Results Survey in Japan involving patients with colorectal cancer reported an increase of 14.04% (AVASTIN Japanese interview form). By comparing the results of this survey with those of the Special Drug Use-Results Survey in Japan, the rates of patients with liver metastasis were 52.20 and 58.98%, respectively, and the rates of patients who had taken antihypertensive drugs were 38.80 and 18.64 %, respectively. In this survey, the rate of patients receiving oral antihypertensive drugs was higher, which may have contributed to the higher incidence of increased blood pressure.

The median frequency of administration in the group with increased blood pressure was three times, and the median cumulative dose was 1,050 mg, but the timing of appearance varies among studies. Some studies reported that the interval until the increase in blood pressure was 4 to 6 weeks (Syrigos et al. 2011), as observed in this survey, whereas others noted a delayed appearance in many patients (Feliu et al. 2015); the definition of an increase in blood pressure in these studies was consistent with that in our survey. There was no association between the increase in blood pressure and the administration period (AVASTIN Special drug use surveillance). Kaplan-Meier curves for the increase in blood pressure demonstrated a significant difference for the presence of liver metastasis in patients without antihypertensive drug, and antihypertensive drug use in patients without liver metastasis. Additionally, the presence of liver metastasis in patients with antihypertensive drug use was significantly associated with increased blood pressure. Although six to seven administrations of bevacizumab led to increased blood pressure in 50% of the patients with at least one risk factor, three administrations of bevacizumab led to increased blood pressure in 50% of the patients with two risk factors at an earlier stage. Therefore, our findings suggest that liver metastasis as well as antihypertensive drug use, which was previously reported, are risk factors for increased blood pressure soon after bevacizumab administration. In particular, patients with both antihypertensive drug use and liver metastasis require careful follow-up because they were found to have increased blood pressure at an earlier stage.

Although there was no significant difference in the association with the dose per session, it was reported to be a risk factor for a marked increase in blood pressure (An et al. 2010). Thus, caution is needed when administering high-dose bevacizumab. Based on multivariate analysis, CRE may be a risk factor for increased blood pressure because blood pressure increases in patients with impaired renal function due to excretory failure of sodium or urine, increased renin secretion, and increased peripheral vascular resistance. Multivariate analysis did not reveal any causal relationship, but univariate analysis indicated significant differences in the BMI and PLT between the groups. The significant difference in BMI may be related to correlations among the distribution volume, clearance, and BMI. On the other hand, we were unable to clarify why there was a significant difference in the PLT. Considering the influence of prior chemotherapy, we conducted a sub-analysis to compare the PLT by dividing the 67 patients into two groups: with and without prior chemotherapy. However, there was no significant difference. In contrast, a previous study reported that thrombocytosis was correlated with the degree of tumor infiltration or metastasis formation in patients with liver metastasis from colorectal cancer (Jósa et al. 2015). This should be further reviewed in the future.

We also examined the influence of sex (female) (Brahmer et al. 2011), which was previously reported as a risk factor, and diabetes

mellitus, which may reduce endothelial nitric oxide synthase (eNOS) activity by vascular endothelial cells being exposed to stress (Vanhoutte et al. 2016; Robinson et al. 2010). However, as the percentage of males was higher and there were few patients with diabetes mellitus, no association was found. Additionally, we investigated sex, body weight, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and albumin (Alb), which were reported to influence the clearance of bevacizumab (AVASTIN Japanese interview form; Lu et al. 2008), but there were no significant differences.

Based on this survey, risk factors for a bevacizumab-induced increase in blood pressure include the presence of liver metastasis and oral administration of antihypertensive drugs, which was previously reported. The findings of this study should be applied to clinical pharmaceutical care.

Our study has some limitations. First, this was a retrospective survey with a limited number of colorectal cancer patients. Additionally, the average SBP at rest before the first bevacizumab administration was significantly higher in patients with an increase in blood pressure than in patients without an increase in blood pressure. Thus, patients with increased blood pressure may be grouped with the patients with a smaller increase in blood pressure. However, the presence of liver metastasis and antihypertensive drug use may be more influential than the SBP at rest before the first bevacizumab administration because they were found to be independent risk factors by multivariate analysis. In the future, the accuracy of prediction must be improved by increasing the number of patients and carcinoma types.

4. Experimental

4.1. Participants

All patients with colorectal cancer for whom bevacizumab (Avastin®, F. Hoffmann-La Roche Ltd, Basel, Switzerland) administration was started at Mazda Hospital of Mazda Motor Corporation (Hiroshima, Japan) between April 2007 and January 2018.

4.2. Definition of an increase in blood pressure

Increased blood pressure was defined as systolic blood pressure (SBP) ≥150 mmHg or diastolic blood pressure (DBP) ≥100 mmHg, which are the same standards as in the clinical trial and Special Drug Use-Results Survey in Japan based on Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

4.3. Inclusion and exclusion criteria

In consideration of our clinical setting, inclusion criteria consisted of: performance status (PS) (Eastern Cooperative Oncology Group, ECOG) ≤2, neutrophils (Neut), platelet count (PLT), total bilirubin (T-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine (CRE) ≤ grade 2 (CTCAE v4.0). These inclusion criteria were selected according to the standards of chemotherapy use set in the Japanese Society for Cancer of the Colon and Rectum Guidelines 2016 for the treatment of colorectal cancer (JSCCR Guidelines 2016).

Exclusion criteria included patients with SBP ≥150 mmHg or DBP ≥100 mmHg before the first bevacizumab administration.

4.4. Survey period and items

This survey was conducted between April 2007 and January 2018. The following items were retrospectively investigated using electronic medical records (1) Blood pressure:

SBP and DBP at rest before bevacizumab administration on each visiting day were measured by patients to avoid white coat hypertension; (2) Status of bevacizumab administration: Frequency of administration and single dosage; (3) Patient characteristics (at the start of administration): Age, sex, height, body weight, PS (ECOG), presence of previous chemotherapy, stage of cancer, presence of liver metastasis or diabetes mellitus, and antihypertensive drug use; (4) Laboratory data (at the start of administration): White blood cell count (WBC), Neut, hemoglobin (Hb), PLT, T-Bil, AST, ALT, alkaline phosphatase (ALP), CRE, creatinine clearance (Ccr), albumin (Alb), lactate dehydrogenase (LDH), hemoglobin A_{1c} (HbA_{1c}), and qualitative assessment of urine protein.

4.5. Statistical analyses

The results were calculated as the mean±standard deviation (S.D.). The Mann-Whitney U-test was used to compare single doses between the groups with or without an increase in blood pressure induced by bevacizumab. SBP and DBP were compared using the Student's t-test. To compare the patient characteristics, the Student's t-test or Fisher's direct probability test was conducted. Laboratory data were compared using the Student's t-test or Mann-Whitney U-test. To extract factors associated with the increase in blood pressure, multivariate analysis (two-value logistic regression analysis) was performed using the increase in blood pressure as the objective variable and the factors extracted by the univariate analysis as explanatory variables. The log-rank test was conducted with Kaplan-Meier curves for the increase in blood pressure with or without the factors extracted by the multivariate analysis. All univariate analyses were carried out using Statcel Ver.2, the multivariate analysis was conducted using Minitab®16, and the log-rank test was performed using EZR (Kanda 2013). A p-value of 0.05 was considered significant.

4.6. Ethical approval

This study was approved by the Medical Ethics Committee of Mazda Hospital of Mazda Motor Corporation.

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Conflicts of interest: None declared.

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AVASTIN Japanese interview form.

AVASTIN Japanese package insert.

AVASTIN Special drug use surveillance.

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