Regular Article

Central Nervous System Ischemia Associated with Bevacizumab: An Analysis of the Japanese Adverse Drug Event Report Database

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Received July 11, 2022; accepted September 23, 2022

Bevacizumab is an inhibitor of vascular endothelial growth factor (VEGF) that prevents tumor growth. While bevacizumab is therapeutically effective, it induces several adverse events. Among these, central nervous system (CNS) ischemia can lead to death or permanent disability. In this study, we reviewed the Japanese Adverse Drug Event Report database to analyze the occurrence of CNS ischemia after bevacizumab administration. Significant associations between the occurrence of CNS ischemia and bevacizumab use were detected (adjusted reporting odds ratios (ROR): 2.68, 95% confidence interval (CI): 2.00–3.59, $p < 0.001$). Furthermore, an association between diagnosis of glioma and bevacizumab use was also detected ($p < 0.001$). These events occurred early after the start of treatment and then gradually decreased; however, more than half of CNS ischemia events were reported beyond 30 d after the first administration. In addition, a logistic regression suggested that CNS ischemia caused by bevacizumab was associated with glioma, underlying hypertension and aging. A poor prognosis was reported for several cases occurring in elderly patients (over 60 years of age). Although bevacizumab is a useful pharmacological treatment for cancer, caution should be taken to avoid severe adverse events. Accordingly, the patient's general and medical condition should be carefully examined before initiating treatment, and blood pressure should be continuously assessed throughout treatment with bevacizumab to prevent CNS ischemia.

Key words bevacizumab; glioma; Japanese Adverse Drug Event Report database; vascular endothelial growth factor; central nervous system ischemia

INTRODUCTION

Bevacizumab is a widely used inhibitor of vascular endothelial growth factor (VEGF) that prevents the development of new tumor-feeding blood vessels and stops tumor growth.[1,2] Although bevacizumab is therapeutically effective, it induces several adverse events, such as hypertension,[3] nephrotic syndrome,[4] bleeding,[5] and thrombosis.[6,7] Bevacizumab inhibits signaling pathways involved in angiogenesis,[8] which may lead to central nervous system (CNS) ischemia,[9] and ultimately permanent disability or death. Avoiding these complications is critical, as they can be even more life-threatening than the underlying cancer.

Several studies have focused on CNS ischemia subsequent to bevacizumab use.[9,10] However, its definitive characteristics have not been elucidated, possibly because of its low incidence and the difficulty in collecting enough cases for analysis. Therefore, we used the Japanese Adverse Drug Event Report (JADER) database in this study, which collects adverse drug reaction data reported voluntarily to the Pharmaceuticals and Medical Devices Agency (PMDA). The JADER has been employed by several previous studies to investigate rare side effects of various drugs.[11–13] In this study, we analyzed the JADER database to determine the incidence and characteristics of CNS ischemia in patients receiving bevacizumab.

MATERIALS AND METHODS

Study Design Data recorded from April 2004 to March 2020 in the JADER database were downloaded from the PMDA website (http://www.pmda.go.jp/). The JADER dataset consists of four tables containing data, including the following: 1) patient information, including sex, age, and body weight; 2) patient drug information; 3) adverse events and outcomes; and 4) medical history and primary illness. These four tables were integrated using the FUND E-Z Backup Archive (FUND E-Z Development Corporation, White Plains, NY, U.S.A.).[12,13] Cases with missing sex or age data were excluded from all analyses in this study. From the data on the drugs administered, the drugs associated with adverse events were categorized into three groups: "suspected drug," "concomitant drug," and "interaction." Drugs classified as a "suspected drug" were examined in the present study. Vascular endothelial growth factor receptor (VEGFR) inhibitors were defined as those in which the route of administration was intravenous. Since temozolomide is used both orally and intravenously,[14] cases using either route of administration were considered together in the analysis.

First, to evaluate the effect of bevacizumab and other VEGF inhibitors (ramucirumab and aflibercept) on the occurrence of drug-induced CNS ischemia, the crude reporting odds ratios (RORs) and the RORs adjusted according to a multivariate analysis were calculated. The interaction of possible factors involved in the development of CNS ischemia was subsequent-

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ly examined. Second, for analysis of possible factors associated with CNS ischemia in patients receiving bevacizumab, the crude and adjusted RORs were calculated with respect to reporting year, age, sex, cancer type, and underlying disorders. Third, to determine factors associated with CNS ischemia in glioma patients, the crude and adjusted RORs were calculated with respect to reporting year, age, sex, drugs, and underlying disorders. Fourth, we investigated outcomes after the development of CNS ischemia associated with bevacizumab. Finally, we investigated the timing of CNS ischemia associated with bevacizumab according to the Weibull distribution.

Definition of Adverse Events and Underlying Disease We used the ICH Medical Dictionary for Regulatory Activities (MedDRA) v 24.0 to extract the adverse events and underlying diseases listed in the JADER database. The detailed definitions of adverse events and underlying disease are provided in Supplementary Table 1. Each patient's underlying disease and cancer type were defined based on the diseases listed in their medical history and primary illness tables. Adverse events were defined as those listed in each patient's adverse events and outcomes tables.

Analysis of the ROR For the analysis of CNS ischemia associated with bevacizumab administration, the crude RORs and 95% confidence intervals (CIs) were calculated. The crude ROR was calculated as follows. First, the cases were classified into four groups, as follows: (a) Individuals who received the drug of interest and exhibited the adverse event of interest; (b) Individuals who received the drug of interest and exhibited other adverse events (of no interest); (c) Individuals who received other drugs (of no interest) and exhibited adverse events of interest; and (d) Individuals who received other drugs (of no interest) and exhibited other adverse events (of no interest). Next, the crude ROR was calculated using the following equation:

$$\text{Crude ROR} = (a/b)/(c/d)$$

$$95\%\ \text{CI} = \exp[\log(\text{ROR}) \pm 1.96\sqrt{(1/a)+(1/b)+(1/c)+(1/d)}\,]$$

The RORs were expressed as point estimates with 95% CIs. The data were analyzed using Fisher's exact test.

We calculated the adjusted ROR similarly the method used in previous reports.[15,16] In addition, the patients were stratified into 0–59 and ≥60 years age groups. To construct the logistic model, sex (male), reporting year, age group, drug, cancer type, and underlying disease were coded. The following logistic model was used for analysis:

$$\text{Log(odds)} = \beta_0 + \beta_1 Y + \beta_2 S + \beta_3 A + \beta_4 D + \beta_5 C + \beta_6 U + \beta_7 S{*}D + \beta_8 A{*}D + \beta_9 C{*}D + \beta_{10} U{*}D$$

Y = reporting year, S = sex, A = stratified age group, D = drug, C = cancer type, U = underlying disease

If more than one drug was present in the same analysis, the adjusted RORs were calculated in independent models for each drug. Furthermore, the adjusted RORs for other factors were calculated using the bevacizumab model.

The results were considered statistically significant at $p < 0.05$. These analyses were performed using JMP 14.0 (SAS Institute, Cary, NC, U.S.A.). A signal was detected when the lower limit of the 95% CI of the adjusted ROR exceeded 1.

Analysis of the Outcome of CNS Ischemia Due to Bevacizumab Administration Cases with complete age and sex data, in which bevacizumab was the suspected drug in the occurrence of CNS ischemia were included in this analysis (319 cases). Cases were classified according to age and outcome, as shown in the graph (Fig. 1). The patient outcomes were determined according to the corresponding entry in the JADER database as "recovered," "remission," "not recovered," "with sequelae" "death" and "unclear."

Analysis of Onset of Adverse Events We selected cases with complete CNS ischemia occurrence and prescription start date information, in which bevacizumab was the suspected causative drug, for the time-to-onset analysis (161/319 cases, 49%). The onset of adverse events was calculated from the time the patient received their first prescription to the occurrence of CNS ischemia. A cut-off period of 365 d after the start of administration was used for the analysis.[17] The me-

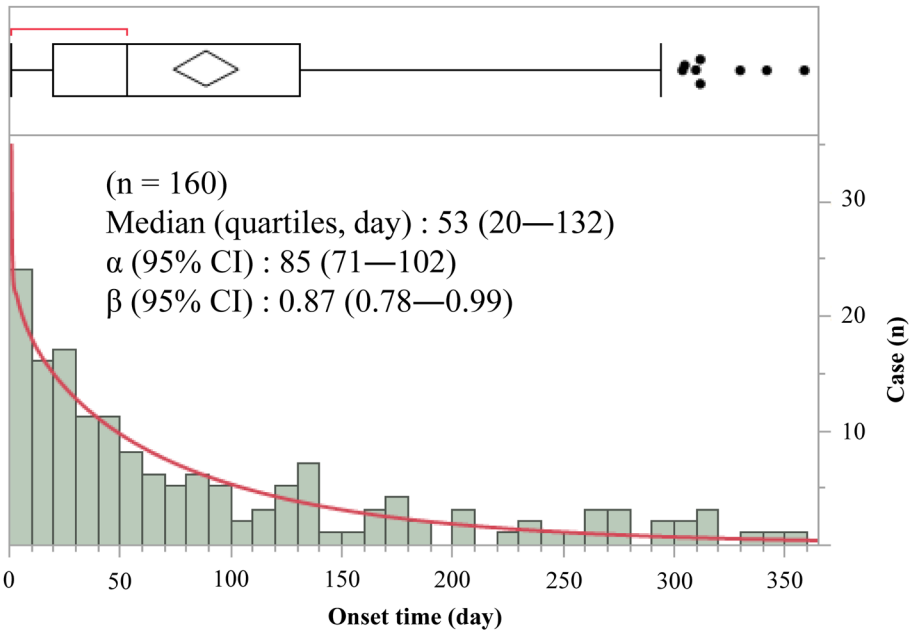

Fig. 1. CNS Ischemia Cases Associated with Bevacizumab in the JADER Database According to Onset Time

dian duration, quartiles (IQR), and Weibull shape parameters were used to evaluate the onset data. The scale parameter α of the Weibull distribution determines the scale of the distribution function: a larger scale value (α) stretches the data distribution, whereas a smaller scale value (α) shrinks the distribution. The Weibull shape parameter β of the Weibull distribution determines the shape of the distribution function: larger and smaller shape values produce left- and right-skewed curves, respectively. The shape parameter, β, of the Weibull distribution was used to indicate the level of hazard over time without a reference population. When β is less than 1 and the upper 95% CI of β less than 1, the hazard is considered to decrease with time. When β is equal to 1, the hazard is estimated to be constant over time. If β is greater than 1 and the lower 95% CI of β greater than 1, the hazard is considered to increase with time.[18] These analyses were performed using JMP 14.0.

RESULTS

Identification of Factors Associated with CNS Ischemia Of the 595121 cases reported between April 2004 and December 2020, 9203 exhibited CNS ischemia. Significant signals related to CNS ischemia were detected among the patients receiving bevacizumab (crude ROR: 2.14, 95% CI: 1.91–2.40, $p<0.001$). In the multivariate logistic regression analysis, significant contributions were observed for bevacizumab (adjusted ROR: 2.68, 95% CI: 2.00–3.59, $p<0.001$), age (≥60 years, adjusted ROR: 1.79, 95% CI: 1.70–1.89, $p<0.001$), reporting year (adjusted ROR: 1.06, 95% CI: 1.06–1.07, $p<0.001$), male sex (adjusted ROR: 1.18, 95% CI: 1.13–1.23, $p<0.001$), glioma (adjusted ROR: 2.09, 95% CI: 1.49–2.92, $p<0.001$), diabetes (adjusted ROR: 1.49, 95% CI: 1.40–1.57, $p<0.001$), hypertension (adjusted ROR: 1.94, 95% CI: 1.84–2.05, $p<0.001$), and dyslipidemia (adjusted ROR: 1.48, 95% CI: 1.38–1.58, $p<0.001$) (Table 1). The interactions between glioma and bevacizumab ($p<0.001$) were also significant.

The Characteristics of Patients with Bevacizumab-Associated CNS Ischemia To evaluate the characteristics of patients with CNS ischemia caused by bevacizumab, we analyzed 9982 cases from the JADER in which bevacizumab was the suspected drug. In multivariate logistic regression analysis, significant contributions were observed for age (≥60 years, adjusted ROR: 1.56, 95% CI: 1.17–2.07, $p=0.002$), glioma (adjusted ROR: 6.69, 95% CI: 4.54–9.85, $p<0.001$), and hypertension (adjusted ROR: 1.72, 95% CI: 1.29–2.30, $p<0.001$) (Table 2).

The Characteristics of CNS Ischemia among Glioma Patients We evaluated the characteristics of CNS ischemia across 1670 cases in the JADER in which glioma was the underlying disease. In the multivariate logistic regression analysis, significant contributions were observed for bevacizumab (adjusted ROR: 4.68, 95% CI: 2.84–7.70, $p<0.001$), hypertension (adjusted ROR: 1.89, 95% CI: 1.02–3.50, $p=0.044$), and reporting year (adjusted ROR: 1.11, 95% CI: 1.02–1.21, $p=0.013$). A significant signal was not detected for temozolomide (adjusted ROR: 0.71, 95% CI: 0.40–1.25, $p=0.24$) (Table 3).

Table 1. Reported Cases of CNS Ischemia and Their Associated RORs in the JADER Database

Characteristic	Total	CNS ischemia	No CNS ischemia	Proportion (%)	Crude ROR (95% CI)	Adjusted ROR (95% CI)	*p*-Value
Total	595121	9203	585918	1.55			
Reporting year	—	—	—	—	—	1.06 (1.06–1.07)	<0.001
Sex, male	306003	5254	300749	1.72	1.26 (1.21–1.32)	1.18 (1.13–1.23)	<0.001
Age ≥60 years	378055	7300	370755	1.93	2.23 (2.12–2.34)	1.79 (1.70–1.89)	<0.001
Cancer type							
Glioma	1670	81	1589	4.85	3.27 (2.58–4.09)	2.09 (1.49–2.92)	<0.001
Breast cancer	13031	140	12891	1.07	0.69 (0.58–0.81)	0.75 (0.64–0.90)	0.002
Cervical cancer	963	7	956	0.73	0.47 (0.19–0.96)	0.46 (0.22–0.97)	0.043
Colon and rectosigmoid cancer	11235	203	11032	1.81	1.18 (1.02–1.35)	0.82 (0.70–0.95)	0.010
Ovarian cancer	3726	43	3683	1.15	0.74 (0.54–1.00)	0.77 (0.56–1.05)	0.094
Small cell lung cancer	13558	138	13420	1.02	0.65 (0.54–0.77)	0.46 (0.39–0.54)	<0.001
Drugs							
Bevacizumab	9982	319	9663	3.20	2.14 (1.91–2.40)	2.68 (2.00–3.59)	<0.001
Ramucirumab	2328	32	2296	1.37	0.89 (0.60–1.26)	0.68 (0.48–0.97)	0.031
Aflibercept	262	5	257	1.91	1.24 (0.40–2.93)	0.96 (0.39–2.32)	0.90
Disease							
Diabetes	62719	1957	60762	3.12	2.33 (2.22–2.46)	1.49 (1.40–1.57)	<0.001
Hypertension	91604	2981	88623	3.25	2.69 (2.57–2.81)	1.94 (1.84–2.05)	<0.001
Dyslipidemia	38764	1375	37389	3.55	2.58 (2.43–2.73)	1.48 (1.38–1.58)	<0.001
Interaction							
Male * bevacizumab	—	—	—	—	—	1.00 (0.78–1.27)	0.97
Age ≥60 years * bevacizumab	—	—	—	—	—	0.85 (0.64–1.13)	0.27
Glioma * bevacizumab	—	—	—	—	—	2.24 (1.38–3.64)	<0.001
Diabetes * bevacizumab	—	—	—	—	—	0.89 (0.61–1.32)	0.57
Hypertension * bevacizumab	—	—	—	—	—	0.95 (0.71–1.27)	0.73
Dyslipidemia * bevacizumab	—	—	—	—	—	0.69 (0.41–1.16)	0.16

ROR, reporting odds ratio; 95% CI, 95% confidence interval; CNS, central nervous system; JADER, Japan adverse drug event report.

Table 2. Reported Cases of CNS Ischemia and Their Associated RORs among Patients Receiving Bevacizumab in the JADER Database

Characteristic	Total	CNS ischemia	No CNS ischemia	Proportion (%)	Crude ROR (95% CI)	Adjusted ROR (95% CI)	*p*-Value
Total	9982	319	9663	3.20			
Reporting year	—	—	—	—	—	0.97 (0.94–1.00)	0.079
Sex, male	5275	189	5086	3.58	1.31 (1.04–1.65)	1.10 (0.85–1.42)	0.47
Age ≥60 years	7029	251	6778	3.57	1.57 (1.19–2.09)	1.56 (1.17–2.07)	0.002
Cancer type							
Glioma	317	46	271	14.5	5.84 (4.08–8.21)	6.69 (4.54–9.85)	<0.001
Breast cancer	1005	16	989	1.59	0.46 (0.26–0.77)	0.70 (0.40–1.24)	0.22
Cervical cancer	227	4	223	1.76	0.54 (0.14–1.41)	0.88 (0.31–2.48)	0.81
Colon and rectosigmoid cancer	3160	120	3040	3.80	1.31 (1.03–1.66)	1.29 (0.99–1.69)	0.058
Ovarian cancer	566	14	552	2.47	0.76 (0.41–1.30)	1.16 (0.63–2.14)	0.62
Small cell lung cancer	956	11	945	1.11	0.33 (0.16–0.60)	0.44(0.23–0.82)	0.010
Disease							
Diabetes	669	35	634	5.23	1.75 (1.19–2.53)	1.25 (0.85–1.84)	0.25
Hypertension	1403	79	1324	5.63	2.07 (1.58–2.70)	1.72 (1.29–2.30)	<0.001
Dyslipidemia	357	20	337	5.60	1.85 (1.10–2.96)	1.02 (0.62–1.70)	0.93

ROR, reporting odds ratio; 95% CI, 95% confidence interval; CNS, central nervous system; JADER, Japan adverse drug event report.

Table 3. Reported Cases of CNS Ischemia and Their RORs among Glioma Patients in the JADER Database

Characteristic	Total	CNS ischemia	No CNS ischemia	Proportion (%)	Crude ROR (95% CI)	Adjusted ROR (95% CI)	*p*-Value
Total	1670	81	1589	4.85			
Reporting year	—	—	—	—	—	1.11 (1.02–1.21)	0.013
Sex, male	914	44	870	4.81	0.98 (0.61–1.58)	0.87 (0.54–1.39)	0.56
Age ≥60 years	832	53	779	6.37	1.97 (1.21–3.27)	1.43 (0.86–2.38)	0.16
Drugs							
Bevacizumab	317	46	271	14.5	6.38 (3.94–10.4)	4.68 (2.84–7.70)	<0.001
Temozolomide	586	18	568	3.07	0.51 (0.28–0.89)	0.71 (0.40–1.25)	0.24
Disease							
Diabetes	91	10	81	11.0	2.62 (1.16–5.36)	1.89 (0.86–4.16)	0.11
Hypertension	200	21	179	10.5	2.75 (1.55–4.73)	1.89 (1.02–3.50)	0.044
Dyslipidemia	82	10	72	12.2	2.96 (1.31–6.10)	1.25 (0.55–2.87)	0.59

ROR, reporting odds ratio; 95% CI, 95% confidence interval; CNS, central nervous system; JADER, Japan adverse drug event report.

Onset Time of Bevacizumab-Associated CNS Ischemia The time-to-onset profiles are depicted in Fig. 1. The onset of drug-induced CNS ischemia was analyzed using a Weibull distribution analysis. The median and quartiles of time to CNS ischemia were 53 (20–132) days, and the scale parameters were $\alpha = 85$, 95% CI: 71–102; $\beta = 0.87$, 95% CI: 0.78–0.99. CNS ischemia occurred beyond 30 d of the start of bevacizumab administration in 64% (103/160) of cases.

The Age and Outcomes of Patients with Bevacizumab-Associated CNS Ischemia Figure 2 shows the outcomes of patients with bevacizumab-associated CNS ischemia, which are summarized according to sex and age. Bevacizumab-related CNS ischemia tended to be more common among male patients. With respect to age, bevacizumab-associated CNS ischemia tended to be more common and more severe in patients ≥60 years.

DISCUSSION

In this study, we used the JADER database to analyze the relationship between bevacizumab and the occurrence of CNS ischemia. Significant signals associated with CNS ischemia were detected in patients receiving bevacizumab. The results also suggested that CNS ischemia was associated with a diagnosis of glioma, underlying hypertension, and aging.

Bevacizumab is a monoclonal antibody that blocks VEGF receptors, thereby inhibiting angiogenesis in cancer cells and stopping tumor growth.[19] However, several adverse events have been reported to result from the inhibition of angiogenesis.[20–22] Among these, CNS ischemia can be a life-threatening adverse event. However, its association with bevacizumab administration has not been clearly elucidated.[23] Several mechanisms underlying the association of CNS ischemia with bevacizumab have been proposed. VEGF increases nitric oxide and prostacyclin production and inhibits pathways involved in endothelial cell activation, apoptosis, and coagulation.[24] Therefore, inhibition of VEGF may cause thrombosis and hemorrhage,[25] thereby impairing the regenerative capacity of endothelial cells. Alternatively, an interesting hypothesis suggests that bevacizumab forms a complex with VEGF that may induce platelet aggregation, degranulation, and thrombosis through activation of the platelet FcγRIIa receptor.[6] These different mechanisms may be related.

This study also examined the occurrence of CNS ischemia in cases where aflibercept and ramucirumab were used, which have VEGF inhibitory effects and are administered intrave-

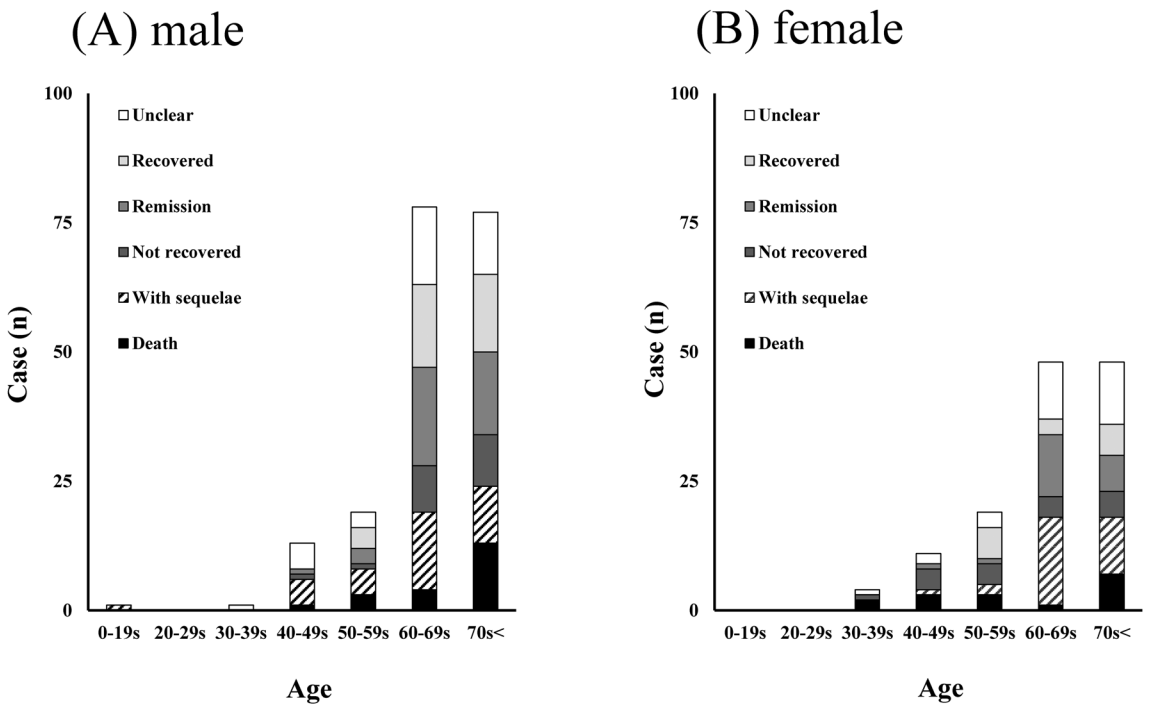

Fig. 2. CNS Ischemia Cases Associated with Bevacizumab in the JADER Database According to Sex, Age, and Outcome
(A) male patients, (B) female patients.

nously, similar to bevacizumab. Although cases have been reported in which these drugs might cause CNS ischemia,[26,27] there have been no large-scale investigative studies, and it is not known whether the risk of CNS ischemia is increased by administration of these drugs. In this study, no significant association between CNS ischemia and drugs other than bevacizumab was observed. Unlike bevacizumab, which only binds to VEGF A, aflibercept binds to VEGF A, B, and C, as well as placental growth factor. Ramucirumab, on the other hand, binds to VEGFR 2.[28] These differences in the affinities of anti-VEGF inhibitors to various growth factors may affect their capacity to cause CNS ischemia.

In this study, an interaction between glioma and bevacizumab was detected. Furthermore, in an analysis of patients with glioma as the underlying disease and those receiving bevacizumab, significant signals were detected in both groups. Bevacizumab is considered to be an effective treatment for glioma, prolonging progression-free survival when administered alone or in combination with cytotoxic agents.[29] However, the incidence of CNS ischemia during bevacizumab treatment has been reported to be somewhat higher in patients with glioma than in patients with other types of cancer.[30–32] The association between glioma and stroke may be the direct result of compression of cerebral blood vessels by the tumor.[33] Radiation and surgery are also commonly used to treat glioma, and both modalities are reportedly associated with the development of CNS ischemia.[34] The effect of gliomas on the surrounding cerebral blood vessels is believed to explain the higher incidence of CNS ischemia in these patients than in those with other cancer types. In addition to these disease-related factors, bevacizumab may affect blood vessels through its VEGF-mediated action, further increasing the risk of CNS ischemia. This study also examined temozolomide, which is considered to be effective against gliomas[35] and is frequently used for this purpose. However, no significant signal of CNS ischemia was detected. Temozolomide is an alkylating agent that acts directly on tumor cells,[36,37] so its mechanism of antitumor action is completely different from that of bevacizumab. These results suggest that bevacizumab may induce CNS ischemia by its own mechanism of action.

Hypertension is recognized as a risk factor for CNS ischemia.[38] It is also a common side effect of bevacizumab, and thus bevacizumab administration increases the severity of hypertension.[39] The presence of hypertension or CNS ischemia can influence the development of cardiovascular disease, and the risk of cardiovascular disease in patients receiving bevacizumab is increased by hypertension.[40] In this study, a significant increase in CNS ischemia was detected in patients with underlying hypertension receiving bevacizumab. Therefore, CNS ischemia may be more likely to occur when bevacizumab is administered to hypertensive patients. However, arterial hypertension occurring during angiogenic therapy (such as using bevacizumab) is reportedly associated with the biological inhibition of VEGF-related pathways, and may be a potential marker of therapeutic efficacy.[41,42] Therefore, instead of discontinuing the use of bevacizumab in the case of elevated blood pressure, it may be necessary to check for background hypertension before starting treatment, and to try to prevent CNS ischemia by closely controlling blood pressure during administration. There was also a trend towards higher RORs of CNS ischemia in the presence of other underlying diseases, such as diabetes and hyperlipidemia, but a significant signal was not detected. Although these diseases are risk factors for CNS ischemia,[43,44] their symptoms may be not affected by bevacizumab. Therefore, the underlying hypertension may play a larger role in the development of CNS ischemia than the other diseases.

Aging has been reported to be a risk factor for CNS isch-

emia,[38] and in this study, among patients receiving bevacizumab, CNS ischemia was more common in the elderly (over 60 years of age). In addition, many of these patients suffered a poor outcome, with the JADER database reporting outcomes of "with sequelae" and "death." Infarctions and post-infarction edema are more likely to be severe in the elderly due to circulatory insufficiency in the collateral blood vessels being more common among these patients.[45] Furthermore, oxidative stress and inflammation subsequent to infarction may be more severe in the elderly, leading to the development of neuroinflammatory disease,[46,47] which is associated with a worse prognosis. Similar mechanisms may be present in bevacizumab-induced CNS ischemia. Therefore, bevacizumab-induced CNS ischemia may also be more likely to occur and to be more severe in the elderly. However, given that diseases affecting the cerebrovascular system, such as diabetes, hypertension, dyslipidemia, and arrhythmia, increase with age, it is unclear whether the aging itself or these pathologies directly affect the development of CNS ischemia. Further studies are needed to clarify this issue.

A time-to-onset analysis was also performed, which showed that bevacizumab-induced CNS ischemia occurred early after the start of treatment and then gradually decreased. However, more than half of CNS ischemia cases were reported 30 d after the first drug administration. Previous case reports have also documented CNS ischemia up to 6 months after the start of administration.[48] These data suggest that patients receiving bevacizumab should be monitored over the long term.

Despite the important findings highlighted in this study, certain limitations must be noted. In terms of the association between glioma and CNS ischemia, the possible effects of surgery and radiation therapy for glioma therapy have been noted[33,34]; however, data pertaining to these two factors are not available in the JADER database. In addition, it was not possible to obtain quantitative age, biochemical test value data, and cancer severity grades. Furthermore, the drug dose was not considered in this study because temporary interruptions or changes in dose may not have been reflected in the database. Moreover, because the cases in the JADER database are spontaneously reported, there may be some reporting bias, as only data on patients presenting with side effects are available. There is a concern that the research data may be derived from a patient group distinct from those generally encountered in daily clinical practice. Therefore, the results of this study need to be further evaluated through cohort studies and randomized controlled trials.

While bevacizumab is an effective treatment for cancer, its use carries the risk of several side effects, with CNS ischemia being associated with a particularly poor prognosis. This study suggests that the development of CNS ischemia may be influenced by bevacizumab use for glioma, a history of hypertension, and aging. Before bevacizumab is administered, the patient's overall condition should be carefully examined and verified, and the blood pressure should be monitored during treatment to prevent CNS ischemia.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials This article contains supplementary materials.

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