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ORIGINAL PAPER

Management of venous thromboembolism in colorectal cancer patients treated with bevacizumab

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Abstract Venous thromboembolism associated with use of a central venous access system is an urgent problem in patients treated with bevacizumab (bev). We investigated the effectiveness of Doppler ultrasound imaging (DUS) in the early detection of catheter-related thrombosis for avoidance of severe venous thromboembolism. Patients with metastatic colorectal cancer received either FOLFOX-4 + bev or FOLFIRI + bev. DUS was performed on the deep venous system for detection of thrombus formation during the initial cycle of treatment, followed by re-evaluation after the third cycle in patients with asymptomatic thrombus formation. All patients were followed up until treatment was interrupted. Median duration of follow-up was 484 days (range 72–574). Among 41 enrolled patients, curable symptomatic thrombosis occurred in one, and asymptomatic thrombosis in 21 (51.2%). Of 21 patients undergoing re-evaluation, thrombi remained without progression in 17 patients, and enlargement in 4 patients. In two of the patients in whom there was progression, pulmonary embolism occurred after the sixth cycle. In the asymptomatic group, no thrombi developed as far as the superior vena cava in any patient. In the cases of progression, thrombotic enlargement was observed in all the 4 patients, with decreased vascular flow in 2. Using DUS, we were able to detect asymptomatic thrombosis in the early cycles of treatment, indicating its potential in the monitoring of venous thrombi. In the event of an enlarging asymptomatic thrombosis developing into the superior vena cava along with decreased vascular flow, careful follow-up and appropriate anticoagulant therapy may be recommended without increased risk of bleeding.

Keywords Venous thromboembolism · Bevacizumab · Colorectal cancer

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Introduction

Bevacizumab (bev) is a recombinant, humanized monoclonal antibody against vascular endothelial growth factor (VEGF). The combination of bev and chemotherapy for first- and second-line treatment of metastatic colorectal cancer has been shown to improve survival [1–4]. Furthermore, a large observational study indicated that use of bev beyond first progression correlated with improved survival [5]. However, use of bev in conjunction with chemotherapy is associated with an increased risk of arterial thromboembolism, and there is also some controversy as to whether bev contributes to the development of venous thromboembolism (VTE) [6]. Pulmonary embolism (PE) occurs in 2–5% of cases where bev and chemotherapy are

used together [1, 3]. A recent meta-analysis of 15 randomized controlled trials [7] found that bev significantly increased risk of VTE in cancer patients and anticoagulant therapy is indicated in the event of VTE.

An implantable central venous access system (CVAS) is a risk factor for VTE [8]. Many VTEs, although asymptomatic, can be as serious as PEs in terms of morbidity [9, 10]. Based on the results of studies on the prevention of catheter-related thrombosis, anticoagulant prophylaxis is not generally recommended with a CVAS [11–13].

In our hospital, symptomatic venous thrombosis associated with a CVAS occurred in patients treated with bev plus chemotherapy during the initial cycle. Appropriate screening and management of patients after detection of either symptomatic or asymptomatic VTE remain to be clarified.

We evaluated the effectiveness of Doppler ultrasound imaging (DUS) in the early detection of CVAS-associated venous thrombosis to determine its potential in the prevention of further development into severe VTE.

Patients and methods

Study design

This was a prospective cohort study conducted at a single institute. Patients were enrolled from July 2007 onward after approval of bev in June 2007 in Japan. The study protocol, including the use of DUS, was approved by the institutional review board of our institute. All the patients provided written informed consent before treatment.

The study design is shown in Fig. 1. DUS was performed on the deep venous system in the upper extremities where catheterization had been carried out to detect thrombus formation during the early cycles of chemotherapy. The first DUS was performed after the initial cycle of bev. Only patients with asymptomatic thrombus formation underwent follow-up evaluation by DUS after the third cycle of bev. During DUS, location and dimension of thrombus, vascular flow, and collateral vascular flow were evaluated and diagnosed by a radiologist at our institute. In addition, dimension of thrombus, location, whether it extended as far as the junction of the external jugular vein (EJV), suprascapular vein (SSV) or subclavian vein (SCV), collateral vascular flow, and retention of peripheral vascular flow were evaluated as important factors directly affecting vascular flow.

At our institute, time to treatment from implantation of a CVAS is usually just 2 days. This made it difficult to perform DUS prior to initiation of treatment and we could not delay treatment for that purpose in the patients enrolled in this study. Therefore, as a subordinate examination, we performed additional pre-treatment DUS between implantation of the CVAS and induction of bev in those patients who consented to the procedure.

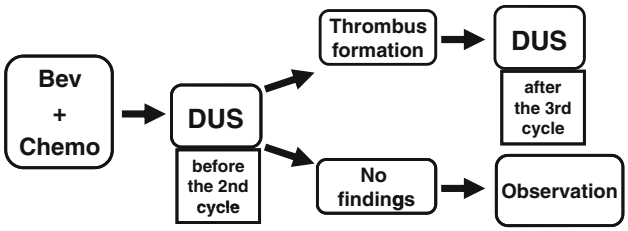

Fig. 1 Timing of DUS: study schema

Patients

All the patients conformed to the following criteria: histologically confirmed colorectal cancer; advanced metastatic colorectal cancer; age $\leq$ 70 years; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; no history of thromboembolic events; no prior use of bev; no increased risk factors for bleeding; hypertension, if present, controlled with a single agent.

All the patients received the initial cycle of treatment when they were in the hospital, and additional treatment cycles at an ambulatory center. Complete blood count, international normalized ratio (INR), and D-dimer were measured biweekly or before treatment in all the patients. Deficiencies of protein C, protein S, and antithrombin III as congenital risk factors for thrombosis were examined, as well as the presence of acquired risk factors before initial bev administration.

Chemotherapy treatment

Treatment regimens were as follows: FOLFOX-4 + bev (biweekly cycles of 85-mg/m^2 intravenous oxaliplatin for 2 h on day 1 plus 100-mg/m^2 L-leucovorin (L-LV) for 2 h and 400-mg/m^2 bolus 5-FU, followed by a 22-h infusion of 600 mg/m^2 5-FU on days 1 and 2, plus 5–10-mg/kg bev on day 1 every 2 weeks); or 5-mg/kg FOLFIRI + bev (biweekly cycles of 150-mg/m^2 intravenous irinotecan for 1.5 h on day 1 plus 200-mg/m^2 L-LV for 2 h and 400-mg/m^2 bolus 5-FU, followed by a 46-h infusion of 1200 mg/m^2 5-FU on days 1 and 2 plus 5-mg/kg bev on day 1 every 2 weeks). Treatment continued until progression, unmanageable toxic effects, or patient refusal. Antiemetic agents were provided at the discretion of the treating physician. No prophylactic use of colony-stimulating factor was permitted. No anticoagulant therapy before initial evaluation by DUS was permitted. If an asymptomatic thrombus that could potentially cause a PE was identified on DUS, anticoagulant therapy was permitted. The anticoagulant treatment regimen was at the discretion of the physician.

Evaluation of toxicity and efficacy

Patient data were recorded and reviewed on electronic clinical records. Adverse effects were graded in all the patients biweekly or before treatment using the National Cancer Institute Common Toxicity Criteria, version 3.0. Cancer response was assessed every 12 weeks using computed tomography according to the response evaluation criteria for solid tumors. Data on toxicity and tumor evaluation were analyzed using electronic medical records and by examination of films of each patient. A radiologist examined the films and made an assessment of status, and the evaluations were recorded in electronic medical records.

Differences in baseline characteristics and clinical features between patients with and without catheter-related thrombosis were analyzed. We used the Chi-square test (without the Yates correction) and Fisher's exact probability test for categorical comparisons of data. Differences in the means of continuous measurements were tested by the Student's t test and checked by Mann–Whitney U test. Quantitative variables such as time between two points were summarized using medians. A two-way repeated-measures analysis of variance was used to evaluate differences between sequential continuous variables. A P value of <0.05 was considered significant.

Results

Characteristics of patients

Forty-one patients were enrolled in the study. The baseline characteristics of the patients are shown in Table 1. Median follow-up time from the date of initial bev administration was 484 days (range 72–574 days). Eight patients (19.5%) received an antihypertensive agent at baseline. In addition, no congenital factors for thrombosis were seen, but anticardiolipin antibody IgG and lupus anticoagulant were observed in 5 (12.2%) and 1 (2.4%) patients, respectively.

Table 1 Baseline characteristics of patients ($N = 41$)

Characteristics	N (%)
Sex: male/female	17/24
Mean age (range), years	58.4 (16–69)
Chemotherapy regimen	
FOLFOX4 + bev 5 mg/kg	28 (68.3)
FOLFOX4 + bev 10 mg/kg	1 (2.4)
FOLFIRI + bev 5 mg/kg	12 (29.3)
ECOG performance status	
0	39 (95.1)
1	2 (4.9)
Treatment set as systemic chemotherapy for metastatic disease	
First-line	28 (68.3)
Second-line	13 (31.7)
Prior adjuvant fluorouracil	5 (12.2)
No. of involved organs	
1	16 (39)
2	19 (46.3)
3	5 (12.2)
4	1 (2.4)
Sites of metastases	
Liver	19 (46.3)
Lung	20 (48.8)
Peritoneum	8 (19.5)
Nodes	17 (41.5)
Local recurrence	7 (17.1)
Bone	1 (2.4)
Previous history/complication	
Thromboembolic events	0
Hypertension	8 (19.5)
Diabetes	2 (4.9)
Hyperlipidemia	1 (2.4)
Hyperuricemia	1 (2.4)
Liver function failure	1 (2.4)
Congenital risk factors	
Protein C deficiency	0
Protein S deficiency	0
Antithrombin III deficiency	0
Acquired risk factors	
Anticardiolipin antibody IgG	5 (12.2)
Anticardiolipin antibody β2-glycoprotein 1	0
Lupus anticoagulants	1 (2.4)

Bev bevacizumab, *ECOG* Eastern Cooperative Oncology Group, *INR* international normalized ratio, *CRP* C-reactive protein, *IgG* immunoglobulin G

Effectiveness of DUS

The results of DUS are shown in Table 2. Catheter-related thrombosis was observed on initial DUS in 22 patients (53.7%), including both asymptomatic ($n = 21$ [51.2%]) and symptomatic ($n = 1$ [2.4%]) thrombi. No thrombus formation was detected in 19 patients (46.3%). Twenty-two patients received a follow-up DUS, one of whom received anticoagulant therapy after initial DUS. Thrombi disappeared completely in 3 (13.6%) of these 22 patients without anticoagulant therapy.

Comparisons of initial and follow-up DUS findings in asymptomatic thrombi are shown in Table 3. In 21 patients with asymptomatic thrombi, none of the thrombi extended to the superior vena cava, and complete disappearance was seen in 3. Thrombus size was <20 mm in 16 patients (76.2%) on initial DUS, compared to in 16 patients (76.2%) on follow-up DUS. Decreased vascular flow was observed

Table 2 Results of DUS ($N = 41$)

Median length, days (range)	
IP-CVAS—induction of bev	7 (2–695)
IP-CVAS—initial DUS	18 (7–700)
Induction of bev—initial DUS	7 (4–14)
Induction of bev—follow-up DUS	35 (14–49)
Results of initial DUS, *n* (%)	
Thrombus formation	22 (53.7)
Symptomatic thrombosis	1 (2.4)
Asymptomatic thrombosis	21 (51.2)
No thrombus formation	19 (46.3)
Results of follow-up DUS ($n = 22$), *n* (%)	
Thrombus formation	19 (86.4)
No thrombus formation (disappeared)	3 (13.6)

IP-CVAS implantation of central venous access system, *bev* bevacizumab

in 3 patients (14.3%) on initial DUS that showed no progression on follow-up DUS; however, another 2 patients in whom adequate vascular flow was detected on initial DUS showed decreased vascular flow on follow-up DUS. We defined overall improvement as at least one improved finding without progression in location, maximum size, or (collateral) vascular flow and progression as at least one progressed finding; those fitting neither category were defined as the remainder. Overall, thrombi improved or remained stable in 17 patients (81%), and progressed without symptoms in 4 patients (19%). Correlations between vascular flow and other findings are shown in Table 4. Incidence of thrombi extending into the junction of the SCV, ECV, and SSV was significantly higher in patients with inadequate vascular flow than in patients with adequate vascular flow on initial DUS (66.7 vs. 5.6%, respectively; $P = 0.0414$) and on follow-up DUS (80 vs. 0%, respectively; $P = 0.0016$).

Symptomatic thrombosis was revealed on DUS in 1 patient (a DUS image with a diagram is shown in Fig. 2). This thrombus extended into the superior vena cava, was >40 mm in diameter, and resulted in decreased vascular flow. This patient received anticoagulant therapy after initial DUS and re-started bev after a follow-up DUS revealed that the thrombus had not progressed.

Characteristics of patients with and without thrombi are shown in Table 5. Median follow-up time from date of initial bev administration was 518 days (range 232–574 days) and 487 days (72–559), respectively, in these patients. No significant difference was observed in performance status or age. Presence of acquired risk factors showed no effect on thrombus formation or outcome in patients with asymptomatic thrombus. Incidence of thrombus formation was significantly higher in the FOLFOX + bev treatment group than in the FOLFIRI + bev group ($P = 0.0047$). Median length of time between implantation of CVAS and induction of bev was significantly shorter in patients with thrombus formation than in patients without thrombus formation (5 vs. 107.5 days, respectively; $P = 0.0048$). Similarly, median length of time between implantation of CVAS and initial DUS was significantly shorter in patients with thrombus formation than in patients without thrombus formation (13.5 vs. 116 days, respectively; $P = 0.0059$). In further follow-up after completion of the protocol, 1 patient in whom no thrombus was detected in the planned DUS experienced asymptomatic thrombosis of the inferior vena cava during the 12th cycle. However, we were able to continue FOLFOX in this patient without bev using warfarin.

A comparison of patients with improved thrombus findings on follow-up DUS ($n = 5$) with those showing thrombus progression ($n = 4$) revealed that median follow-up time from date of initial bev administration was 505 days (range 446–563 days) and 395.5 days (range 256–484 days), respectively. No significant differences were observed in findings on initial DUS, median time to induction of bev from implantation of CVAS (5 vs. 6 days; $P = 0.9004$), or laboratory data between the two groups. The results of a two-way repeated-measures analysis of variance to evaluate differences between sequential continuous variables such as platelet count, INR, and D-dimer showed no significant differences. Changes in thrombus size, as well as decreased vascular flow, were mainly related to outcomes of thrombus on initial DUS. However, two patients showing thrombus progression developed pulmonary embolism requiring urgent treatment with a thrombolytic agent followed by warfarin, after which, they were able to continue with FOLFOX without bev until progression of disease. None of the patients experienced sequelae, including post-thrombotic syndrome, and there were no deaths related to thromboembolic events or anticoagulant therapy.

Discussion

In this study, we assessed the effectiveness of DUS in the early identification of catheter-related thrombosis and variations in asymptomatic venous thrombosis under use of bev.

According to the American Society of Clinical Oncology [14], the presence of a central venous catheter is a risk factor for VTE in cancer patients. Active chemotherapy [15, 16] and antiangiogenic therapy [2, 3] also carry risk of VTE. With the newer antiangiogenic agents, the use of a prophylaxis for VTE is controversial [2, 3, 17, 18].

Although a CVAS makes it easier to administer chemotherapy in ambulatory patients, its use is associated with

Table 3 Findings associated with asymptomatic thrombosis ($n = 21$)

Findings	Initial DUS	Follow-up DUS
Location, *n* (%)		
Distal (not extended to SVC)	21 (100)	18 (85.7)
Central (extended to SVC)	0	0
Comparison	Improved (disappeared) in 3 patients (14.3)	
Maximum size, *n* (%)		
0–<10 mm	14 (66.7)	12 (57.1)
10–<20 mm	2 (9.5)	4 (19)
20–<30 mm	3 (14.3)	3 (14.3)
>30 mm	2 (9.5)	2 (9.5)
Comparison	Improved in 5 patients (23.8) (disappeared in 3 and reduced in 2)	
	Progressed in 4 patients (19)	
Vascular flow, *n* (%)		
Adequate	18 (85.7)	13 (61.9)
Inadequate	3 (14.3)	5 (23.8)
Comparison	Improved in 3 patients (14.3)	
	Progressed in 2 patients (9.5)	
Collateral vascular flow, n (%)		
Adequately increased	2 (9.5)	2 (9.5)
Inadequately increased	1 (4.8)	3 (14.3)
Comparison	Progressed in 2 patients (9.5)	
Overall evaluation[a]	Improved in 5 patients (23.8)	
	Stable in 12 patients (57.1)	
	Progressed in 4 patients (19)	

[a] Overall improvement was defined as at least one improved finding without progression in location, maximum size, or (collateral) vascular flow and progression as at least one progressed finding; those fitting neither category were defined as the remainder. One patient receiving anticoagulant therapy after initial DUS showed a thrombus 45 mm in diameter that developed into the brachiocephalic vein; no progression was noted. One patient with thrombus progression experienced a symptomatic pulmonary embolism after the sixth cycle, and one progressed patient experienced an asymptomatic pulmonary embolism after the sixth cycle

SVC superior vena cava

Table 4 Correlation between vascular flow and other findings of asymptomatic thrombosis ($n = 21$)

Findings on DUS	Initial DUS ($n = 21$)		Follow-up DUS ($n = 18$)	
	Adequate ($n = 18$)	Inadequate ($n = 3$)	Adequate ($n = 13$)	Inadequate ($n = 5$)
Location, *n* (%)				
SCV–ECV–SSV junction[a]	1 (5.6)	2 (66.7)	0	4 (80)
P value	0.0414		0.0016	
Maximum size, *n* (%)				
<30 mm	18(100)	1 (33.3)	13 (100)	3 (60)
≥30 mm	0	2 (66.7)	0	2 (40)
P value	0.0143		0.0654	

[a] Thrombi extended into junction of SCV, ECV, and SSV in two inadequate patients at initial DUS; both thrombi sizes were ≥30 mm

DUS Doppler ultrasound imaging, *SCV* subclavian vein, *ECV* external jugular vein, *SSV* suprascapular vein, *N.A* not applicable

an increased risk for VTE and PE [8–10]. According to a review by Vescia et al. [19], the incidence of catheter-related thrombosis varied from 12 to 64% in four retrospective studies [20–24]. In a recent prospective trial using phlebography in patients with a CVAS, Verso et al. [25] found that the incidence of thrombosis in two groups receiving low molecular weight heparin (LMWH) or placebo for 6 weeks was 14.1 and 18%, respectively (95% CI 0.47–1.31; $P = 0.35$), with symptomatic upper limb thrombosis seen only in 1.0% of the LMWH group and 3.1% of the placebo group (hazard ratio 0.32; 95% CI 0.07–1.66). In another trial by Couban et al. [12], the rate of symptomatic thrombosis in a group received 1-mg warfarin for 9 weeks was 4.6% when compared with 4.0% in the placebo group (hazard ratio 1.20; 95% CI 0.37–3.94).

We summarized thromboembolic events reported in nine pivotal studies of bev plus chemotherapy [1–4, 17, 18, 26–28]. According to the results, the incidence of thromboembolism ranged from 3 to 26% in these studies, and PE was reported in 1–4% of cases. Prophylactic anticoagulant treatment was not permitted in any study, except for maintenance of CVAS in four studies [1, 2, 4, 18].

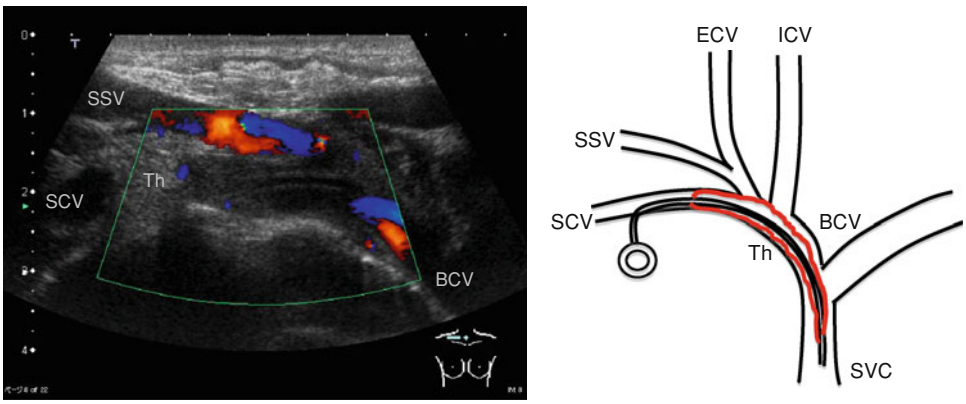

Fig. 2 Findings of DUS image and illustration in symptomatic case. This thrombus (Th) extended into superior vena cava (SVC) through brachiocephalic vein (BCV), was >40 mm in diameter, and resulted in clearly decreased vascular flow

Table 5 Comparison between patients with and without thrombus formation

	With thrombus ($n = 22$)	Without thrombus ($n = 19$)	*P* value
Sex: male/female	9/13	8/11	>0.9999
Mean age (range), years	62 (16–69)	60.1 (47–69)	0.9896
ECOG performance status, *n* (%)			
0	22 (100)	17 (89.5)	0.2308
1	0	2 (10.5)	
Chemotherapy regimen, *n* (%)			
FOLFOX4 + bev	20 (90.9)	9 (47.4)	0.0047
FOLFIRI + bev	2 (9.1)	10 (52.6)	
Prior treatment, *n* (%)			
FOLFOX	2 (9.1)	10 (52.6)	0.0047
Hepatic arterial infusion	3 (13.6)	4 (21.1)	0.6847
Radiation	3 (13.6)	0	0.2354
No. of involved organs, *n* (%)			
1/2/3/4	10/10/2/0	6/9/3/1	0.3899
≥3	2 (9.1)	4 (21.1)	
Baseline laboratory data, mean ± SD			
Platelets ($\times 10^4$ μl)	22.6 ± 5.68	18.89 ± 6.84	0.0652
INR	1.05 ± 0.49	1.05 ± 0.12	0.9811
D-dimer	1.15 ± 1.52	1.21 ± 0.83	–
Acquired risk factors, *n* (%)			
Anticardiolipin antibody IgG	3 (13.6)	2 (10.5)	>0.9999
Lupus anticoagulants	1 (4.5)	0	>0.9999
Median length (range), *n* (%)			
IP-CVAS—induction of bev	5 days (2–252)	107.5 days (2–695)	0.0048
IP-CVAS—initial DUS	13.5 days (7–259)	116 days (7–700)	0.0059

ECOG Eastern Cooperative Oncology Group, *bev* bevacizumab, *INR* international normalized ratio, *IP-CVAS* implantation of central venous access system, *DUS* Doppler ultrasound imaging, *SD* standard deviation

According to these studies, the incidence of thromboembolic events was not high and routine prophylactic anticoagulant treatment for thromboembolism did not appear necessary.

Patient characteristics in our study were similar to those in previous reports, and no specific characteristics related to thrombus formation were seen. However, we observed a higher rate of thrombi than expected using DUS and almost all of them were asymptomatic. Indeed, this study was designed to detect diagnostic findings, not clinical findings.

This study had a number of limitations. First, there was no control population (with no administration of bev). In other words, thromboembolic events may have been due to prior chemotherapy rather than bev, as only small doses of bev had been given at first screening. Second, the study protocol did not provide true baseline DUS at pre-treatment, as the time to treatment from implantation of the CVAS was usually just 2 days or more. Therefore, it was difficult to establish whether there was a correlation between the treatment drugs and catheter-related thrombosis, or when

thrombus formation occurred, as a CVAS itself is a risk factor for VTE.

However, we did perform DUS at pre-treatment between implantation of the CVAS and induction of bev in a limited number (17) of the patients. The characteristics of these 17 patients showed no differences to those of the other enrolled patients. Of these 17 patients, asymptomatic thrombosis was detected in 5 (29.4%). Of the other 12 patients, 5 showed asymptomatic thrombosis on initial DUS. Treatment with bev was probably associated with thrombus formation in these 5 patients, with incidence lower than that in the total study population (41.7 vs. 53.7%). The characteristics of these 5 patients were also similar to those of the general study population, and their outcomes consisted of a stable thrombus in 3 and asymptomatic progression in 2. The results indicate that a CVAS-associated thrombus prior to induction of bev was not necessarily a significant risk factor for severe thromboembolism.

When comparing the thrombus group with the non-thrombus group, the shorter the time between implantation of CVAS and induction of bev, the greater the risk of thrombus formation, regardless of whether it was symptomatic or asymptomatic. Moreover, a statistically significant difference in thrombus formation was observed between FOLFOX and FOLFIRI (90.9 vs. 9.1%; $P = 0.0047$). However, we do not believe that variation of drugs in FOLFOX versus FOLFIRI was associated with incidence of catheter-related thrombosis, as FOLFOX was used as first-line therapy with implantation of the CVAS, and FOLFIRI as second-line therapy in patients who already had a CVAS. No significant difference in laboratory data was observed between patients receiving FOLFOX and those receiving FOLFIRI; moreover, a shorter time between implantation of the CVAS and induction of bev showed no correlation with poor prognosis of thromboembolism. This point is of particular importance for the physician in treating patients with a bev-based regimen. Therefore, we hypothesized as follows: inhibition of either VEGF or cyclooxygenase (COX)-2-dependent prostacyclin (PGI2) biosynthesis associated with bev may have abolished a tonic protective pathway, thereby increasing the risk of thrombosis. VEGF binds to its major endothelial receptor, kinase insert domain-containing receptor (KDR) or VEGF receptor-2, triggering activation of endothelial nitric oxide synthase (eNOS) and COX-2, enzymes that mediate production of nitric oxide (NO) and PGI2. Bev would interrupt the pathway by which NO and PG12 inhibit platelet aggregation and proliferation of vascular smooth muscle cells, thus increasing risk of thrombosis and arterial wall thickening [29, 30]. Fibroblast growth factor (FGF-2) is quickly released during the wound-healing process, providing an early stimulus for endothelial cell proliferation in the acute phase immediately after injury. FGF-2 appears to be able to up-regulate VEGF production and acts synergistically in stimulating angiogenesis. Platelet-derived growth factor, transforming growth factor-3 and local hypoxia may also regulate VEGF production. Consequently, VEGF increases gradually from the third day after injury onward, providing a sustained stimulus for endothelial cell migration and differentiation into new capillary tubes [31]. Based on these previous reports, we believe that induction of bev in the early phase after implantation of a CVAS may be associated with high risk of thrombus formation due to a low level of VEGF production.

The strength of this study is its prospective assessment of catheter-related thrombus formation using DUS, a highly sensitive and non-invasive strategy. Routine prophylactic anticoagulant treatment at baseline, or if asymptomatic thrombosis was detected, was not permitted; this provided us with the opportunity to evaluate asymptomatic thrombus formation without the influence of prophylactic drugs. The results showed that outcomes in patients with asymptomatic thrombosis mainly depended on changes in thrombus size, as well as decreased vascular flow. In addition, vascular flow appeared to deteriorate with increase in thrombus size.

Our findings indicate that an enlarging thrombus, or large thrombus (>40 mm in diameter), along with decreased venous flow, is a risk factor for symptomatic thromboembolism or PE. Accordingly, we have started to administer prophylactic anticoagulant treatment in such patients at this facility. Further examination of venous flow revealed that thrombi extending into the junction of the SCV, ECV, or SSV strongly affected vascular flow. This finding may furnish an indirect marker of decreased vascular flow.

The American Society of Clinical Oncology provides guidelines on the prevention of recurrent VTE in oncology patients [14]. LMWH is the preferred initial approach for established VTE, and is also preferred in long-term prevention (>6 months). Vitamin K antagonists are an option when LMWH is not available. In Japan, LMWH has not been approved, and unfractionated heparin is used as initial therapy, followed by long-term warfarin therapy with a targeted INR of 2–3.

In conclusion, we propose that routine prophylactic anticoagulant treatment should not be used in patients treated with bev, as bev can increase the risk of bleeding. Therefore, it is important to assess eligibility for bev before treatment and during routine follow-up using available strategies to prevent severe thromboembolism. The results of this study indicate that a period of 1 week or more should be left between introduction of an IP-CVAS to administration of bev to reduce thrombus formation. DUS may offer the optimum strategy for detection of asymptomatic thrombosis in the early cycles of treatment. Moreover,

detection of an enlarging asymptomatic thrombosis developing into the superior vena cava along with decreased vascular flow or extending into the junction of the SCV, ECV, or SSV by DUS may be predictive of subsequent severe symptomatic thromboembolism. Large randomized controlled trials are needed to investigate the mechanism of VTE associated with bev and optimal management of this problem.

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