Hypoalbuminemia for the prediction of venous thromboembolism and treatment of direct oral anticoagulants in metastatic gastric cancer patients

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Abstract

Background Venous thromboembolism (VTE) is highly associated with advanced gastric cancer (AGC) and is sometimes lethal. Predictors of VTE have not been identified, and the efficacy and safety of direct oral anticoagulants (DOACs) for AGC-associated VTE remain to be clarified.

Methods A total of 188 AGC patients who started chemotherapy during the period from January 2014 to December 2017 in our institutions were retrospectively examined for the incidence of VTE, risk factors for VTE, and the efficacy and safety of DOAC-based anticoagulant therapy for VTE.

Results Thirty-four patients (18%) were diagnosed with VTE at the start or during the course of chemotherapy (VTE group). More VTE group patients had a history of abdominal surgery and had moderate–severe ascites (32% versus 17%, 32% versus 14%, respectively) than non-VTE group patients (NVTE group). The mean serum albumin concentrations in the VTE group were significantly lower than NVTE group (3.38 mg/dL vs 3.65 mg/dL, respectively). Multivariate analysis showed that hypoalbuminemia was significantly correlated with VTE ($P=0.012$). In the VTE group, 29 patients (85%) received anticoagulant therapy, including 24 patients treated with DOACs. No lethal VTE was observed in any patients. Thirteen patients (45%) terminated DOACs because of anemia or bleeding events, of whom eleven developed major bleeding. Median overall survivals of the VTE and NVTE groups were 9.63 months and 11.5 months, respectively ($P=0.262$).

Conclusion Hypoalbuminemia appears to be a risk factor for AGC-associated VTE. DOACs are effective to AGC-associated VTE, but careful observation of bleeding events is required.

Keywords Venous thromboembolism · Gastric cancer · Hypoalbuminemia · Direct oral anticoagulants · Bleeding

Introduction

Gastric cancer (GC) is a serious disease, the incidence of which is the fifth highest among cancers in the world, and it is the third most common cause of cancer death [1]. Non-resectable advanced and/or recurrent GC (AGC) patients have been treated with chemotherapy. Cytotoxic agents including platinum, fluoropyrimidine, taxane, and irinotecan are administered. Anti-HER2 agents are also used [2]. Additionally, the efficacy of antiangiogenic inhibitor ramucirumab and immune checkpoint inhibitor nivolumab has been proven [3–5]. These agents extended median overall survival (OS) to 13 months in the recent clinical studies [6, 7] however, the prognosis of AGC patients remains poor.

Appropriate control of comorbidities is required to perform chemotherapy. Since AGC is often diagnosed in

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elderly patient, the high incidence of venous thromboembolism (VTE) may be related to their general condition, such as reduced major organ functions. Cancer cells have been known to produce soluble factors, such as tissue factor, that enhance coagulation activity and cause VTE [8]. The incidence of VTE was reported to be 3.5–24.4%, and it was higher in AGC patients than in those with other cancers [9–12].

Park et al. reported that the incidence of VTE in AGC was 17.5% in their prospective observational study [10]. Khorana et al. demonstrated that VTE was the major cause of mortality in cancer outpatients [13]. The mortality of cancer patients with VTE was two times higher than that of cancer patients without VTE [14].

Chemotherapies also cause venous diseases [15]. Therefore, appropriate prevention and control of vascular diseases themselves, in addition to anti-cancer treatments, are thought to contribute to prolonging survival of AGC patients. Although guidelines recommend administering anticoagulants to prevent vascular diseases in advanced cancer patients [16–18], the absolute indication for anticoagulants in cancer patients has not been clarified. Risk factors for VTE include poor general condition, having cancer including AGC, and chemotherapy. Although D-dimer has been recognized as a sensitive laboratory test for predicting VTE, a previous study reported that the pretreatment D-dimer level was only a marginal risk factor for developing VTE [10]. The Khorana score is a predictive risk assessment model for VTE in cancer patients [19]. However, some reports showed that the Khorana score were not able to stratify VTE risk [20, 21]. Thus, a standard predictive method for VTE still remains to be clarified, especially for AGC patients.

Acute VTE is treated with anticoagulant therapy including unfractionated heparin, vitamin K antagonists, and low-molecular weight heparin (LMWH). LMWH has been the standard treatment for VTE in patients with cancer [16–18]. However, LMWH is not approved for VTE in Japan. Recent clinical studies reported that direct oral anticoagulants (DOACs) were non-inferior to LMWH with respect to the composite outcome of recurrent venous thromboembolism for cancer-associated VTE [22–24]. On the other hand, side effects of DOACs such as bleeding should be carefully controlled along with cancer treatments. However, the actual impact of the side effects of DOACs in the treatment of AGC patients, who often suffer bleeding events from the remaining primary site, and their use in AGC patients who have difficulties with oral ingestion have not been well assessed. Thus, the effectiveness of DOACs for VTE in AGC patients and their survival benefit have not been clarified. The present study aimed to examine the incidence of VTE, risk factors for VTE development, therapeutic methods for VTE and their efficacy, especially of DOACs, based on data from clinical practice.

Patients and methods

Patients

The present study examined the 188 consecutive patients who were diagnosed with AGC and were administered first-line chemotherapy during the period from January 2014 to December 2017 in the National Kyushu Cancer Center (Fukuoka, Japan). Clinical information was retrospectively collected via electronic medical records. Follow-up was performed to May 2018. Inclusion criteria were as follows: histologically proven gastric or esophago-gastric junctional adenocarcinoma, unresectable metastases or recurrence, measurable lesions or evaluable lesions, started first-line chemotherapy for AGC at our hospital, organ function adequate to receive chemotherapy, and written, informed consent for the chemotherapy. Patients with VTE at the start of first-line chemotherapy and receiving treatment for the VTE were allowed. Recurrent GC patients during adjuvant chemotherapy or less than 6 months after final administration of adjuvant chemotherapy were excluded. The amount of ascites was defined as mild (limited to the pelvic cavity or around the liver), moderate (neither mild nor severe), or severe (continuous ascites from the surface of the liver to the pelvic cavity) by computed tomographic (CT) scan. The present study protocol was approved by the local ethics committee of the National Kyushu Cancer Center according to the guidelines for biomedical research specified in the Declaration of Helsinki. Informed consent was not obtained from each patient due to the retrospective nature of the present study.

Chemotherapy

The initial chemotherapy for the AGC patients was basically performed according to the treatment guideline issued by the Japanese Gastric Cancer Association [2]. Combinations of oral fluoropyrimidine and platinum were frequently used. For patients with HER2-positive GC, trastuzumab was administered in combination with the doublet cytotoxics, fluoropyrimidine and platinum, following the standard chemotherapy regimen. Tumor response was examined generally by CT every 2 or 3 months. Chemotherapy was continued until clinical or radiological progression of the disease, intolerable adverse events, patient's wish, or decision of the attending physician. Subsequent chemotherapy was administered to the patients for whom it was indicated.

Diagnosis and treatments for VTE

Venous thromboembolism was classified in three groups: extremity venous thrombosis (EVT); intra-abdominal venous thrombosis (IVT); and pulmonary thromboembolism (PE). EVT of the pelvis and lower extremities was classified in two types, proximal type and peripheral type. In proximal type, the center of the thrombus was located in the iliac vein, femoral vein, and popliteal vein. In the peripheral type, the center of the thrombus was located in the anterior tibial vein, posterior tibial vein, fibular vein, gastrocnemius vein, and soleus muscle vein. Diagnosis of VTE was performed radiologically by contrast-enhanced CT or vascular ultrasonography.

Treatments for VTE were performed according to the clinical practice guideline for VTE issued by the Japanese Circulation Society [25]. The therapeutic agent was selected based on the status of VTE. Concurrent or subsequent warfarin, unfractionated heparin, and DOACs were used for the treatment of VTE. A venous filter was placed for patients at high risk of pulmonary embolism and difficulties with anticoagulant therapy. Anticoagulant treatment was continued until serious side effects or loss of efficacy. In accordance with the criteria of the International Society on Thrombosis and Haemostasis (ISTH), major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of ≥ 2 g/dL, led to a transfusion of ≥ 2 units of blood, occurred at a critical site, or contributed to death [26].

Statistical analyses

The statistical significance of differences in characteristics between the VTE group and the non-VTE group was assessed using the χ^2 test or the t test. Correlations between clinical characteristics and the development of VTE were analyzed by logistic regression analysis. Covariates with P values < 0.05 on univariate analysis were included in the multivariate analysis with backward elimination using the Wald statistic. OS was calculated by the Kaplan–Meier method from the date of AGC diagnosis to the date of death or last follow-up. Survival was compared using the log-rank test. All analyses were two-tailed, with $P < 0.05$ considered significant. All statistical procedures were performed using SPSS Statistics software version 21 (IBM Japan, Tokyo, Japan).

Results

Patients

A total of 188 AGC patients were included in this study (Table 1). The median age of the patients was 66 years

(range 27–85 years). There were 124 male (66%) and 64 female (34%) patients. Histologically, adenocarcinoma was diagnosed in 185 patients (98.4%). Of the whole patient population, 34 patients (18.1%) were diagnosed with VTE prior to or during the period of chemotherapy (VTE group), and the other 154 patients (81.9%) did not show any evidence of VTE (NVTE group). No significant differences in age, sex, performance status (PS), and body mass index (BMI) between the VTE group and the NVTE group were found. In terms of items related to the primary gastric tumor, histological type, disease status (metastatic vs recurrent), primary tumor resection, and number of metastatic organs were not significantly correlated with VTE. AGC patients with moderate–severe ascites showed a trend to have VTE (32.4% versus 14.3%). There were no significant differences between the VTE and NVTE groups in comorbidities including hypertension and diabetes mellitus and a history of neoplasms. Previous intraperitoneal surgery was more frequent in the VTE group than in the NVTE group (32.4% vs 16.9%). The Khorana score and laboratory parameters (white blood cell, platelet, hemoglobin, C-reactive protein and D-dimer) were no significant differences between the VTE and NVTE groups. Interestingly, a low serum concentration of albumin was observed at a significantly higher frequency in the VTE group.

Risk factors for VTE

On univariate analysis of clinical characteristics affecting VTE development, ascites (moderate–severe vs none–mild, odds ratio (OR) 2.87, 95% CI 1.23–6.70, $P = 0.015$), previous intraperitoneal surgery (yes vs no, OR 2.34, 95% CI 1.02–5.38, $P = 0.046$) and serum concentration of albumin (OR 0.42, 95% CI 0.21–0.82, $P = 0.012$) were found to be associated with VTE development (Table 2). Multivariate analysis was performed with these three factors, and the serum concentration of albumin was significantly associated with VTE development (OR 0.42, 95% CI 0.21–0.83, $P = 0.012$) (Table 2).

Diagnosis of VTE

The characteristics of the 34 patients with VTE are shown in Table 3. EVT was the most frequent diagnosis, and 30 of 34 patients (88.2%) had pelvic or lower extremity type venous thrombosis. Among them, the proximal type and the peripheral type were observed in 12 patients (35.2%) and 18 patients (52.9%), respectively. Two patients (5.9%) had internal jugular/subclavian/brachiocephalic vein thrombosis. IVT was observed in one patient (2.9%), and PE was observed in eight patients (23.5%). In the 34 VTE patients, 26 (76.5%) showed EVT alone, four (11.8%) showed EVT + PE, one (2.9%) showed EVT + PE + IVT,

Table 1 Patients' characteristics

Characteristic	No. of patients (%)			<i>P</i> value
	All <i>N</i> = 188	Non-VTE <i>N</i> = 154	VTE <i>N</i> = 34	
Age (years)				
Median (range)	66 (27–85)	66 (32–85)	66 (27–85)	
< 65	77 (41.0)	65 (42.2)	12 (35.3)	0.458
≥ 65	111 (59.0)	89 (57.8)	22 (64.7)	
Sex				0.077
Male	124 (66.0)	106 (68.8)	18 (52.9)	
Female	64 (34.0)	48 (31.2)	16 (47.1)	
ECOG PS				0.513
0–1	163 (86.7)	133 (86.4)	30 (88.2)	
≥ 2	25 (13.3)	21 (13.5)	4 (11.8)	
Body mass index (kg/m ²)				0.189
< 25	164 (88.3)	132 (87.0)	32 (94.1)	
≥ 25	22 (11.7)	20 (13.0)	2 (5.9)	
Histology				0.449
Adenocarcinoma				
Well to moderately differentiated	38 (20.2)	33 (21.4)	5 (14.7)	
Poorly differentiated	147 (78.2)	120 (77.9)	27 (79.4)	
Others	3 (1.6)	1 (0.6)	2 (5.9)	
Disease status				0.290
Metastatic	154 (81.9)	124 (80.5)	30 (88.2)	
Recurrent	34 (18.1)	30 (19.5)	4 (11.8)	
Prior tumor surgery				0.257
Yes	35 (18.6)	31 (20.1)	4 (11.8)	
No	153 (81.4)	123 (79.9)	30 (88.2)	
Metastatic site				
Liver	68 (36.2)	59 (39.3)	9 (26.5)	0.193
Lung	17 (9.0)	14 (9.1)	3 (8.8)	0.961
Peritoneum	99 (52.7)	78 (50.6)	21 (61.8)	0.240
Lymph node	105 (55.9)	83 (53.9)	22 (64.7)	0.251
Bone	24 (12.8)	18 (11.7)	6 (17.6)	0.346
No. metastatic sites				0.776
1	57 (30.3)	46 (29.9)	11 (32.4)	
≥ 2	131 (69.7)	108 (70.1)	23 (67.6)	
Ascites				0.012
None–mild	155 (82.4)	132 (85.7)	23 (67.6)	
Moderate–severe	33 (17.6)	22 (14.3)	11 (32.4)	
Comorbidities				
Hypertension	57 (30.3)	45 (29.2)	12 (35.3)	0.486
Diabetes	23 (12.2)	21 (13.6)	2 (6.9)	0.262
Previous embolic history	22 (11.7)	18 (11.7)	4 (11.8)	0.990
Previous cancer history	16 (8.5)	13 (8.4)	3 (8.8)	0.942
Previous intraperitoneal surgery	37 (19.7)	26 (16.9)	11 (32.4)	0.042
No. of comorbidities				0.302
0	98 (52.1)	83 (53.9)	15 (44.1)	
≥ 1	90 (47.9)	71 (46.1)	19 (55.9)	
Khorana score				0.690
Low risk	0	0	0	
Intermediate risk	115 (61.2)	95 (61.7)	20 (58.8)	

Table 1 (continued)

Characteristic	No. of patients (%)			<i>P</i> value
	All <i>N</i> = 188	Non-VTE <i>N</i> = 154	VTE <i>N</i> = 34	
High risk	71 (37.8)	57 (37.0)	14 (41.2)	
Laboratory parameters				
WBC mean (range, / μ L)	6790 (2730–15,540)	6784 (2730–15,540)	6816 (3040–14,500)	0.947
Platelet mean (range, 10^9 /L)	26.8 (5.3–61.1)	27.0 (6.3–61.1)	25.9 (5.3–49.3)	0.281
Hb mean (range, g/dL)	11.7 (5.9–19.6)	11.8 (6.3–19.6)	11.4 (5.9–16.3)	0.590
Albumin mean (range, g/dL)	3.60 (1.9–4.7)	3.65 (2.3–4.7)	3.38 (1.9–4.7)	0.010
CRP mean (range, mg/dL)	1.82 (0.07–23.1)	1.92 (0.07–23.1)	1.39 (0.07–12.2)	0.434
D-Dimer mean (range, μ g/mL)	3.48 (0.5–34.2)	3.44 ^a (0.5–34.2)	3.66 ^b (0.5–15.5)	0.889

VTE venous thromboembolism, ECOG Eastern Cooperative Oncology Group, PS performance status, WBC white blood count, Hb hemoglobin, CRP C-reactive protein

^a*N* = 72 (excluded the patents who had not been tested for D-dimer)

^b*N* = 13 (excluded the patients who had not been tested for D-dimer or with VTE synchronous with AGC at diagnosis)

Table 2 Univariate and multivariate analyses of clinical characteristics associated with development of VTE

Variable	Univariate analysis			Multivariate analysis		
	OR	[95% CI]	<i>P</i> value	OR	[95% CI]	<i>P</i> value
Age (≥ 65 vs < 65 years)	1.34	0.62–2.90	0.459			
Sex (female vs male)	1.96	0.92–4.18	0.080			
ECOG PS (≥ 2 vs 0–1)	0.84	0.27–2.64	0.771			
BMI (≥ 25 vs < 25 kg/m ²)	0.41	0.09–1.86	0.249			
Histology (poor vs well to mod)	1.46	0.53–4.16	0.451			
Disease status (recurrent vs metastatic)	0.55	0.18–1.68	0.296			
Prior tumor surgery (yes vs no)	0.53	0.17–1.61	0.263			
Liver metastasis (yes vs no)	0.58	0.25–1.33	0.197			
Lung metastasis (yes vs no)	0.97	0.26–3.57	0.961			
Peritoneum metastasis (yes vs no)	1.57	0.74–3.37	0.242			
Lymph node metastasis (yes vs no)	1.57	0.73–3.39	0.253			
Bone metastasis (yes vs no)	1.62	0.59–4.44	0.350			
No. of metastatic site (1 vs ≥ 2)	0.89	0.40–1.98	0.776			
Ascites (moderate–severe vs none–mild)	2.87	1.23–6.70	0.015			
Hypertension (yes vs no)	1.32	0.63–2.90	0.485			
Previous embolic history (yes vs no)	1.01	0.32–3.19	0.990			
Previous cancer history (yes vs no)	1.05	0.28–3.91	0.942			
Previous intraperitoneal surgery (yes vs no)	2.34	1.02–5.38	0.046			
No. of comorbidities (≥ 1 vs 0)	1.48	0.70–3.13	0.303			
Khorana Score (moderate risk vs high risk)	1.17	0.55–2.50	0.690			
White blood cell count	1.00	1.00–1.00	0.947			
Platelet count	0.99	0.95–1.03	0.588			
Hemoglobin	0.91	0.77–1.08	0.280			
Albumin	0.42	0.21–0.82	0.012	0.42	0.21–0.83	0.012
C-reactive protein	0.95	0.83–1.08	0.438			
D-Dimer ^a	1.01	0.90–1.13	0.887			

VTE venous thromboembolism, ECOG Eastern Cooperative Oncology Group, PS performance status, BMI body mass index, OR odds ratio

^aExcluded the patients who had not been tested for D-dimer or with VTE synchronous with AGC at diagnosis

Table 3 Characteristics of patients with VTE at the time of diagnosis of VTE

	No. of patients (%) (<i>N</i> = 34)
Site of VTE	
EVT	
Pelvic/lower extremities	30 (88.2)
Proximal type/peripheral type	12 (35.2)/18 (52.9)
Internal jugular/subclavian/brachiocephalic venous thrombosis	2 (5.9)
IVT	1 (2.9)
PE	8 (23.5)
Type of VTE	
EVT only	26 (76.5)
EVT + PE	4 (11.8)
EVT + PE + IVT	1 (2.9)
PE only	3 (8.8)
Diagnostic opportunity	
Symptom	12 (35.3)
Incidental	22 (64.7)
Synchronous VTE with AGC at diagnosis	
Yes	12 (35.3)
No	22 (64.7)
Number of treatment regimens before VTE development	
0	12 (35.3)
1	18 (52.9)
≥ 2	4 (11.7)
Chemotherapy regimen before VTE	
Fluorouracil	21 (61.8)
Cisplatin	15 (44.1)
Oxaliplatin	5 (14.7)
Paclitaxel	5 (14.7)
Trastuzumab	1 (2.9)
Ramucirumab	1 (2.9)
D-Dimer	
Elevated D-dimer	33 (97.1)
Unknown	1 (2.9)
Median (μg/mL) (range)	8.98 (1.31–424)

VTE venous thromboembolism, EVT extremity venous thrombosis, IVT intra-abdominal venous thrombosis, PE pulmonary thromboembolism, AGC advanced gastric cancer

and three (8.8%) showed PE alone. Of these 34 patients with VTE, 12 (35.3%) had some symptoms, and 22 (64.7%) did not show any symptoms of VTE. VTE prior to chemotherapy for AGC was seen in 12 patients (35.4%), and VTE developed in the other 22 patients (64.7%) after initiation of chemotherapy. The number of chemotherapy regimens before the development of VTE was one in 18 patients (52.9%) and more than two in four patients (11.7%). Anti-HER2 drug therapy and ramucirumab were administered to one patient each. Thirty-three of 34 patients with VTE (97.1%) showed abnormally high levels of D-dimer, and one patient was not examined for D-dimer; the median value of D-dimer was 8.98 μg/mL (1.31–424 μg/mL).

Treatment for VTE

Of the 34 patients with VTE, 29 (85.3%) were treated for VTE, and the course of VTE was observed without anticoagulant therapy in the other five patients (Table 4). These five patients did not receive anticoagulant therapy because they had hemorrhagic primary sites, which might develop severe bleeding with anticoagulant therapy. In the 29 patients treated for VTE, a DOAC alone was administered in 16 patients (47% of the treated patients), unfractionated heparin followed by DOAC was given to seven patients, and fondaparinux and warfarin followed by DOAC were given to one patient. In DOAC, apixaban, edoxaban and rivaroxaban were given to 13, 9 and 2 patients, respectively. Only four

Table 4 Treatment for VTE

	No. of patients (%) (<i>N</i> = 34)
Treatment	
Medication	29 (85.3)
DOACs	16 (47.0)
Unfractionated heparin-DOACs	7 (20.6)
Warfarin	4 (11.8)
Unfractionated heparin	1 (2.9)
Fondaparinux-warfarin-DOACs	1 (2.9)
Inferior vena cava filter	1 (2.9)
No treatment	5 (14.7)
Efficacy of treatments (<i>N</i> = 29 ^a)	
Resolved PE ^b	7 (87.5)
Resolved EVT ^c	16 (57.1)
Resolved IVT ^d	1 (100)
Recurrence	0 (0)
Not evaluated	13 (44.8)
Discontinuation of anticoagulant therapy for bleeding or worsening of anemia (<i>N</i> = 29 ^a)	
Yes	13 (44.8)
No	16 (55.2)
Causes of death (<i>N</i> = 28 ^c)	
Disease progression	27 (96.4)
Intracranial bleeding	1 (3.7)
VTE	0 (0)

VTE venous thromboembolism, DOACs direct oral anticoagulants, PE pulmonary thromboembolism, EVT extremity venous thrombosis, IVT intra-abdominal venous thrombosis

^aOnly the patients on anticoagulant therapy

^b*N* = 8

^c*N* = 28

^d*N* = 1

^eFive patients are alive, and one patient is unknown

patients (11.8% of the treated patients) received warfarin alone, and one patient received unfractionated heparin alone. In one patient, an inferior vena cava filter was placed because bleeding from the primary site complicated the administration of anticoagulant therapy, palliative gastrectomy was planned, and he had high-risk proximal type EVT possibly causing PE. Fifteen patients (51.7%) received anticoagulant therapy for longer than three months, and six patients (20.7%) received it for longer than six months. The median duration of oral anticoagulant therapy was 3.2 months.

None of the 34 VTE patients developed fatal VTE. All eight patients who had PE received anticoagulant therapy, and seven of them showed the disappearance of PE on CT. The median time for disappearance of PE was 2.4 months (range 1.1–5.1 months). The other patient died from primary tumor before evaluation of the efficacy of anticoagulant therapy. Sixteen of 29 patients treated for EVT showed

amelioration or disappearance of thrombus detected by CT or venous ultrasonography of the lower extremities.

Anticoagulant therapy was terminated because of bleeding symptoms or progression of anemia in 13 patients (44.8%), and 11 patients (37.9%) showed major bleeding. The median duration of therapy for the 13 patients was 2.4 months (range: 0.03–18.7 months). These cases included bleeding from the primary tumor in eight patients, brain hemorrhage in one patient, gastrointestinal bleeding from other than the primary site in one patient, and hematuria in two patients (Table 5). Disseminated intravascular coagulation occurred in one patient. All 13 patients who terminated anticoagulant therapy showed improvement of anemia after termination of the therapy. Even after termination of the therapy, no recurrence of clinically remarkable VTE was observed. Twenty-eight of 34 VTE patients died, 27 (96.4%) from primary tumor progression and one (3.6%) from brain hemorrhage.

Overall survival and VTE

The median OS of the total 188 AGC patients was 11.3 months (95% CI 9.6–13.1 months). The median OS of the VTE group (*N* = 34) was 9.63 months, and that of the NVTE group (*N* = 154) was 11.5 months, with no significant difference between them (*P* = 0.262) (Fig. 1a). The median OS of the patients who had VTE at the initial diagnosis of AGC was 8.8 months, and that in patients with VTE diagnosed after chemotherapy was 9.6 months (*P* = 0.092), with no significant difference between them. The median OS after the diagnosis of VTE was 5.7 months.

Discussion

The present study showed the frequent development of VTE in AGC patients and that hypoalbuminemia appears to be an independent risk factor for VTE. Additionally, DOACs seemed to be effective for AGC-associated VTE, but bleeding events were quite high. To our knowledge, this is the first study to show hypoalbuminemia as a risk factor for VTE and the efficacy and safety of DOACs in AGC homogeneous patients.

AGC is a frequent cause of tumor-associated VTE. A prospective, observational study examining 241 AGC patients showed that the incidence of VTE was 17.5% [10]. The investigators suggested that the relatively high incidence of VTE might be caused by high tumor burden, but remaining primary tumor and number of metastatic organs were not correlated with the incidence of VTE [10]. Another study by Lee et al. reported that the incidence of VTE in patients harboring early stage GC and advanced stage GC was 0.5–3.5% versus 24.4% [12]. Chemotherapy also causes

Table 5 Characteristics of 13 patients who developed bleeding during anticoagulant therapy

Case	Primary tumor	Primary site	Borrmann type	Anticoagulant agent	Duration of anti-coagulant therapy (months)	Source of bleeding	Major bleeding	OS from discontinuation of anti-coagulant therapy (months)
1	Present	U	2	Fondaparinux-warfarin-edoxaban	18.7	Primary tumor	(+)	2.5
2	Present	UM	2	UFH-edoxaban	8.2	Primary tumor	(+)	8.1
3	Present	L	0	Edoxaban	5.7	Genitourinary	(-)	4.3
4	Present	ECJ	2	UFH-apixaban	3.5	Primary tumor	(+)	1.1
5	Absent	—	—	Apixaban	2.7	Genitourinary	(+)	3.0
6	Present	ML	4	UFH-rivaroxaban	2.5	Primary tumor	(+)	1.4
7	Present	L	3	UFH-apixaban	2.4	Primary tumor	(+)	3.6
8	Present	UML	4	Edoxaban	1.7	Unknown	(+)	0.03
9	Present	UM	4	Warfarin	1.6	Intracranial	(+)	0.4
10	Present	ML	2	Apixaban	1.2	Primary tumor	(+)	11.3
11	Present	UM	2	Apixaban	0.2	Primary tumor	(+)	8.3
12	Absent	—	—	Edoxaban	0.2	GI (unknown)	(-)	5.1 (alive)
13	Present	ML	3	UFH	0.03	Primary tumor	(+)	8.4

U upper part, M middle part, L low part, ECJ esophago-cardiac junction, GI gastrointestinal

Fig. 1 Kaplan–Meier plots for overall survival (OS). **a** OS curves of patients with or without venous thromboembolism (VTE). **b** OS curves of patients with VTE diagnosed at the initial diagnosis of

advanced gastric cancer (AGC) and those with VTE diagnosed after the start of chemotherapy

VTE in tumor-bearing patients [19]. Park et al. showed that the cumulative number of VTEs increased for 15 months after initiation of chemotherapy, and the median time to onset of VTE was 3.9 months [10]. Lee et al. also reported that the incidence of VTE was significantly higher in the first 3 months after the start of chemotherapy [12]. The present study showed that the incidence of VTE was 18.1% after the diagnosis of AGC. The rates of patients who had

primary tumor or who had two or more metastatic organs among all patients were almost similar to those reported by Park et al. [10]. The median time to onset of VTE was 2.4 months, which was also similar to the previous study [10, 12]. These findings for VTE are thought to be reproducible in AGC patients.

Since VTE affects cancer patients' survival, intensive anticoagulant therapy is usually performed at least for VTE

that appeared during chemotherapy. In the present study, 85.2% of VTE patients received anticoagulant therapy, except for a few patients with a higher risk of bleeding, and no significant correlation between the development of VTE and survival was observed. No correlation between VTE and AGC patients' survival was also reported in the previous studies [10, 11]. These observations suggest that adequate anticoagulant therapy for AGC patients who had VTE during chemotherapy might maintain survival almost equivalent to that in NVTE patients. Additionally, the VTE patients in the present study were thought to have received appropriate anticoagulant therapy. On the other hand, the relatively short OS of AGC patients may cause difficulty in detecting differences in survival due to the development of VTE. Because the present study was retrospective and had a limited number of AGC patients, the actual impact of VTE on the survival of AGC patients has still not been confirmed.

D-dimer has been suggested to be a predictor of VTE. Park et al. reported that D-dimer could be a marginally significant risk factor for VTE development [10]. In the present study, D-dimer did not show a significant correlation with VTE. Previous studies reported that D-dimer elevated in cancer patients with absence of VTE and high D-dimer level was associated with poor prognosis [27–29]. Potential mechanism of D-dimer elevation in malignancy might associated with circulating tumor cells clots [30]. The present findings and the previous reports suggest that D-dimer is not a predictor of VTE in AGC patients. Additionally, Khorana score consists of five variables; primary cancer site, pre-treatment platelet count, hemoglobin, leucocyte count, and BMI, which were correlated with the development of VTE [19]. Arai et al. also reported that only BMI was a risk factor for VTE [11]. However, our study showed that the Khorana score was no correlation with the development of VTE in AGC patients.

In the present study, hypoalbuminemia was interestingly identified as a factor related to the development of VTE. In a prospective observational cohort study of 1070 patients with various tumors including AGC, hypoalbuminemia was significantly associated with increased risk of VTE [31]. A serum albumin concentration > 4 g/dL was shown to be associated with a low risk of VTE in ambulatory patients with non-hematologic malignancies [32]. Several studies reported that hypoalbuminemia was shown to be an independent risk factor for VTE in the general public [33] and patients with nephrotic syndrome [34]. However, these studies did not reveal whether hypoalbuminemia is not only a VTE risk factor but also a direct cause for VTE, because hypoalbuminemia may reflect inflammation [35] and urinary loss of albumin in kidney disease [34], which were reported the association with VTE [34, 35]. The mechanism by which hypoalbuminemia directly leads to the occurrence of VTE has not been elucidated yet. Several previous studies

suggest that albumin affects blood coagulation system. Pear M et al. revealed significant anticoagulant properties of albumin in vitro [36]. According to this study, albumin inhibits the deposition of platelets in the primary hemostasis and impairs fibrinogen activity by interacting with fibrinogen [36]. Maclof J et al. showed that albumin inactivates thromboxane A₂, which is capable of inducing platelet aggregation, directly through binding [37]. Nicholson et al. reported that albumin binds to antithrombin, thereby neutralization of coagulation factor Xa is enhanced [38]. Therefore, these studies suggest that hypoalbuminemia may reflect a hypercoagulable tendency and cause the development of VTE. In the clinical setting, we should consider potential interactions for the influence of albumin on the coagulant system. However, at least in this study, only hypoalbuminemia was recognized as a factor related to the development of VTE. In addition, Königsbrügge et al. reported that hypoalbuminemia is associated with increased risk of VTE independently from kidney or liver function and inflammation marker [31]. The present findings and the previous reports strongly suggest that hypoalbuminemia is a risk factor for the development of VTE in AGC patients.

The present study demonstrated the effectiveness of DOAC therapy for VTE in AGC patients. Rivaroxaban was compared with the standard therapy, which consisted of enoxaparin followed by warfarin, in a randomized clinical study of cancer patients who developed VTE [22]. The rivaroxaban group showed the equivalent incidence of recurrent VTE to that of the standard therapy group. Additionally, the incidence of severe bleeding was lower in the rivaroxaban group than in the standard therapy group. Similar results were reported with respect to the other DOAC, apixaban [23]. These data suggest that DOACs could be used instead of LMWH for the treatment of VTE.

Guidelines recommend continuing anticoagulant therapy such as LMWH for cancer-associated VTE for at least 3–6 months [16–18]. Although the risks of VTE remain in patients with advanced cancer, and ongoing chemotherapy makes physicians consider continuation of anticoagulant therapy for a longer period, the appropriate period of anticoagulant therapy has not been clarified. A randomized clinical study comparing the recurrence rate of VTE and the incidence of major bleeding in cancer patients with VTE between treatment with 6–12 months of edoxaban and that with dalteparin was reported [24]. Although the recurrence rate of VTE was lower in the edoxaban group than in the dalteparin group, major bleeding occurred more frequently in the edoxaban group than in the dalteparin group (6.9% versus 4.0%, HR 1.77, 95% CI 1.03–3.04; $P=0.04$). Patients with upper gastrointestinal bleeding were often observed in the edoxaban group, possibly due to the fact that the edoxaban group included more patients harboring upper gastrointestinal cancers than the dalteparin group (6.3% versus

4.0%). Additionally, the incidence of major bleeding six months after the start of anticoagulant therapy was 5.6% in the edoxaban group vs 3.2% in the dalteparin group.

Previous studies reported that one of 37 AGC patients with VTE died from VTE-related respiratory failure despite anticoagulant therapy [11]. Since severe VTE did not develop in any AGC patients with VTE in the present study, anticoagulant therapy with DOACs might be effective to prevent exacerbation of VTE. On the other hand, major bleeding was seen in 37.9% of AGC patients treated with anticoagulant therapy, and the median time to occurrence of VTE after the start of anticoagulant therapy was 2.4 months (range 0.03–18.7 months). Thus, AGC was frequently associated with VTE, and the risk of major bleeding was also quite high. The indications and duration of anticoagulant therapy for AGC patients with VTE are important, but no study examining the efficacy and safety of anticoagulant therapy with DOACs in patients specifically with AGC has been previously reported. The present study is the first to examine these issues of DOACs in AGC, and further investigation is still needed.

The present study demonstrated the frequent development of VTE in AGC patients and that hypoalbuminemia appears to be a risk factor for VTE. DOACs seemed to be effective for AGC-associated VTE, but bleeding events should be carefully considered with anticoagulant therapy.

Compliance with ethical standards

Conflict of interest M. Kono has received grants from Pfizer Japan Inc. M. Fukata has received grants from Shino-Test Corporation; personal fees from Pfizer, Daiichi Sankyo Company, Bayer Yakuhin, and Boehringer Ingelheim. T. Esaki has received grants and personal fees from Eli Lilly, Taiho, Daiichi-Sankyo, Merck Serono, and Ono; grants from Novartis, DS pharma, MSD and Boehringer; personal fees from Chugai, Bristol, Eisai and Takeda. K. Akashi has received grants and personal fees from Mitsubishi Tanabe Pharma Corporation, Daiichi-Sankyo, MSD, Eisai, Astellas Pharma, Sanofi, Chugai Pharmaceutical, Asahi Kasei Pharma, Kyowa Hakko Kirin, Sumitomo Dainippon Pharma, Bristol-Myers Squibb, Takeda Pharmaceutical, Novartis Pharma, Alexion Pharmaceuticals, Teijin Pharma, Nippon Shinyaku, Yakult Honsha, Mundipharma and Bayer Yakuhin; grants from Ono Pharmaceutical, Merck Serono, Toyama Chemical, Taiho Pharmaceutical, Otsuka Pharmaceutical, Yakult Honsha Co, AbbVie, Shionogi, Eli Lilly Japan, Taisho Toyama Pharmaceutical, Mochida Pharmaceutical, The Chemo-Sero-Therapeutic Research Institute., Merck Serono, Nippon Kayaku, Japan Blood Products Organization, and Shin Nippon Biomedical Laboratories; personal fees from Celgene, Janssen Pharmaceutical, Pfizer, Medical Review, Amgen Astellas Biopharma and Shire Japan. E. Baba has received grants, personal fees and non-financial support from Eli Lilly Japan; grants and personal fees from Daiichi-Sankyo, Bristol-Myers Squibb, Taiho Pharmaceutical, Eisai, Yakult Honsha, and Ono Pharmaceutical; grants from Bayer Yakuhin, MSD, Linical; personal fees from Takeda Pharmaceutical, Sumitomo Dainippon Pharma, Kyowa Hakko Kirin, Sanofi, Merck Serono, Tsumura, Chugai Pharmaceutical, and Astellas Pharma. All of the remaining authors declare that they have no conflicts of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

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