EUROPEAN JOURNAL OF CANCER 48 (2012) 492–500

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Venous thromboembolism (VTE) in patients with advanced gastric cancer: An Asian experience

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ARTICLE INFO

Article history:
Available online 12 December 2011

Keywords:
Venous thromboembolism (VTE)
Advanced gastric cancer (AGC)
Incidence rate
Overall survival
Prognosis

ABSTRACT

Background: The incidence and prognostic impact of venous thromboembolism (VTE) in patients with advanced gastric cancer (AGC) have not been determined. We therefore investigated the incidence of VTE and the clinical characteristics associated with VTE in AGC patients treated with systemic chemotherapy.

Patients/Methods: We retrospectively evaluated the incidence of VTE in 3095 patients diagnosed with inoperable AGC in the Department of Oncology at the Asan Medical Center.

Results: We found that the 1-year cumulative incidence of VTE was 3.5% and incidence rate was 1.88 events/100 person-years (95% confidence interval, 1.54–2.28 events/100 person-years). Overall survival (OS) was poorer in patients concurrently diagnosed with AGC and VTE than in patients with VTE detected after AGC diagnosis (median OS, 4.5 months versus 10.7 months; HR, 2.171; 95% CI, 1.2–3.93; $P = 0.009$). Multivariate analysis identified female sex, primary tumour site on the upper portion of stomach (cardia/fundus versus body/antrum), two or more metastatic sites, lung metastasis and increased baseline CA19-9 level as independent risk factors for VTE. OS rates were significantly lower in patients with than without VTE (1-year OS, 40% versus 45.3%; 2-year OS, 10.5% versus 19.3%; HR, 1.23; 95% CI, 1.0–1.52; $P = 0.048$). Multivariate analysis, however, showed that VTE was not a statistically significant factor affecting survival ($P = 0.82$).

Conclusions: The incidence rate of VTE was lower in Korean than in Caucasian patients with AGC. VTE was not an independent prognostic factor, although patients with VTE detected at the time of AGC diagnosis had markedly poorer prognosis.

1. Introduction

Venous thromboembolism (VTE), including pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT), is a common complication and leading cause of death in cancer patients.[1] Large, population-based studies have shown that patients with cancer have a four-to seven-fold increased risk of developing VTE compared with patients without cancer.[2,3] In addition, rates of cancer-associated VTE in general appear to be steadily increasing, particularly since the 1990s.[4]

The occurrence of VTE has important implications for patients with malignancy. Several studies have demonstrated that the presence of VTE is an independent predictor of poor survival in patients with cancer.[5–7] Pathophysiologically, cancer cells may induce thrombosis by triggering several

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.11.016

complex prothrombotic pathways. These may include a procoagulant effect of tissue factor expressed by tumour cells, the release of cytokines, the inhibition of fibrinolysis and the overexpression of membrane adhesion molecules.[8–10]

Several risk factors have been identified as contributing to VTE in cancer patients. The primary tumour site strongly affects the risk of VTE, with gastrointestinal (GI) cancers being associated with a high incidence of thromboembolic events.[4] Among tumour types, gastric cancer has been associated with the fifth highest rate of DVT or pulmonary thromboembolism (PE),[11] and a retrospective cohort study reported that the rate of VTE was 7.4% among patients admitted for gastric cancers. [12]

Chemotherapy is another important risk factor for VTE in cancer patients. Chemotherapy may damage the vascular endothelium, cause a disequilibrium between procoagulant and anticoagulant molecules, induce apoptosis of tumour endothelial cells, activate cytokines and increase tissue factor activity.[13] Although it is generally thought that VTE is common in patients receiving palliative chemotherapy, VTE rates have not been well defined in prospective clinical trials. In gastric cancer, the rates of VTE associated with chemotherapy have been found to range from 5.3% to 11.4% in phase II clinical trial, with relatively few phase III data being available.[14–17]

In the clinical practice setting, rates of VTE would be high in patients with advanced gastric cancer (AGC), especially during chemotherapy. Most patients diagnosed with inoperable AGC receive palliative chemotherapy, but there have been few studies on the incidence of VTE in patients with AGC. We therefore assessed the incidence of VTE, its risk factors, and its impact on patient overall survival (OS) in a large cohort of patients with AGC treated with systemic chemotherapy.

2. Materials and methods

2.1. Databases

We retrospectively examined the records of patients diagnosed with AGC and treated in the Department of Oncology at the Asan Medical Center, Seoul, Korea. These databases contain prospectively collected information on all AGC patients who received systemic chemotherapy between January 2000 and December 2008.

2.2. Patients

Patients with histologically confirmed adenocarcinoma of the stomach or oesophagogastric junction, metastatic or recurrent disease after curative surgical resection and those who received adequate follow-up for at least 8 weeks were included. Patients who presented initially with brain metastasis, those who were treated with warfarin before being diagnosed with AGC and those who received radiotherapy, underwent major surgery or experienced significant traumatic injuries within 4 weeks prior to enrolment were excluded. This study was approved by Asan Medical Center Institutional Review Board, the official ethics committee.

2.3. Identification of VTE

VTE is usually defined as DVT of an upper or lower extremity or PTE. VTE was radiologically diagnosed, by Doppler ultrasonography (USG), computerised tomography (CT), CT angiography and/or ventilation/perfusion scan. Patients with superficial phlebitis in upper or lower extremities, those with arterial thrombosis and patients with incidentally identified intra-abdominal thrombosis (of the portal, splenic, renal or mesenteric vein) on abdominal pelvic CT and resulting from direct tumour invasion or thrombus were excluded. Central venous catheter-related thromboses were also excluded.

2.4. Statistical analysis

Incidence rates were calculated as both cumulative incidence and as person-time (events/100 person-years) along with 95% confidence intervals (CI). The time to VTE was measured from the date of diagnosis of AGC to the date of diagnosis of VTE. 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 variables found to be significant on univariate analyses were entered into a multivariable stepwise Cox regression model, with the exception of variables having missing data. For all analyses, two-sided P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Study population

Over the 9-year period from January 2000 to December 2008, a total of 3095 patients with AGC treated at the Asan Medical Center met the inclusion criteria and were included in this analysis. Of those patients, 3085 patients (99.7%) received at least one cycle of palliative chemotherapy; 1569 patients (50.7%) had first-line chemotherapy, 836 (27%) had second-line and 680 (22%) received more than third-line palliative chemotherapy. The remaining 10 patients (0.3%) could not tolerate or refused palliative chemotherapy. Patient characteristics are summarised in Table 1.

3.2. Incidence of VTE

The 1-year and 2-year cumulative incidences of VTE were 3.5% and 4.9%, respectively among the entire AGC cohort. The incidence rate of VTE was 1.88 events/100 person-years (95% CI, 1.54–2.28 events/100 person-years). The median time from diagnosis of AGC to VTE was 4.6 months (range, 0–41 months). Of the 103 VTE patients, 15 (14.6%) were diagnosed with VTE at the diagnosis of AGC, whereas 88 (85.4%) developed VTE after cancer diagnosis, either during or after chemotherapy.

Of the 103 patients diagnosed with VTE, 93 (90.3%) had received more than one cycle of chemotherapy, with 79 (76.7%) receiving fluorouracil and cisplatin-containing chemotherapy before VTE development. Seventy-four patients (71.8%) presented with symptoms of a VTE, whereas 29 (29%) were

Table 1 – Patient characteristics.

Characteristic	No. of patients (%)			P
	All (N = 3095)	non-VTE (N = 2992)	VTE (N = 103)	
Age (years)				
Median (range)	57 (18–88)	57 (18–88)	56 (21–80)	.759
Age (<65)	2259 (73)	2186 (73.1)	73 (70.9)	.623
(⩾65)	836 (27)	806 (26.9)	30 (29.1)	
Gender				
Male	2042 (66)	1986 (66.4)	56 (54.4)	.011
Female	1053 (34)	1006 (33.6)	47 (45.6)	
ECOG PS				
0–1	2367 (76.5)	2292 (76.6)	75 (72.8)	.373
2	728 (23.5)	700 (23.4)	28 (27.2)	
Primary tumour site on stomach				
Cardia/fundus/diffuse	209 (6.8)	192 (6.4)	17 (16.5)	.002
Body	842 (27.2)	801 (26.8)	41 (39.8)	
Antrum	1177 (38)	1140 (38.1)	37 (35.9)	
Unknown	867 (28)	859 (28.7)	8 (7.8)	
Histology (differentiation)				
Well/moderately differentiated	717 (23.2)	690 (23.1)	27 (26.2)	.509
Poorly differentiated/signet ring cell	1677 (54.2)	1604 (53.6)	73 (70.9)	
Mucinous adenocarcinoma	21 (0.7)	21 (0.7)	0	
Unknown	680 (22)	677 (22.6)	3 (2.9)	
Disease status				.885
Initially metastatic	2083 (67.3)	2013 (67.3)	70 (68)	
Recurrent	1012 (32.7)	979 (32.7)	33 (32)	
Number of metastatic site				<.001
1	2195 (70.9)	2174 (72.4)	21 (20.4)	
⩾2	900 (29.1)	818 (27.3)	82 (79.6)	
Metastatic site				
Liver	741 (23.9)	712 (23.8)	29 (28.2)	.308
Peritoneum	1262 (40.8)	1212 (40.5)	50 (48.5)	.103
Lung	151 (4.95)	121 (4)	30 (29.1)	<.001
LNs	1062 (34.3)	989 (33.1)	73 (70.9)	<.001
Bone	188 (6.1)	172 (5.7)	16 (15.5)	<.001
Measurable disease				
Yes	1361 (44)	1310 (43.8)	51 (49.5)	.249
No	1734 (44)	1682 (56.2)	52 (50.5)	
Previous surgery history (including curative or palliative surgery)				.745
Yes	1491 (48.2)	1443 (48.2)	48 (46.6)	
No	1604 (51.8)	1549 (51.8)	55 (53.4)	
Palliative chemotherapy				
Yes	3085 (99.7)	2992 (100)	93 (90.3)	<.001
No	10 (0.3)	0 (0)	10 (9.7)	
Number of chemotherapy				
1st-line	1569 (50.7)	1529 (51.1)	40 (38.8)	<.001
⩾2nd-line	1516 (49)	1463 (48.9)	53 (51.4)	
Baseline laboratory parameters				
Haemoglobin ⩽10 g/dL	661 (21.4)	636 (21.3)	25 (24.3)	.463
>10 g/dL	2434 (78.6)	2356 (78.7)	78 (75.7)	
WBC $\leqslant 11 \times 10^9$/L	2866 (92.6)	2776 (92.8)	90 (87.4)	.039
$>11 \times 10^9$/L	229 (7.4)	216 (7.2)	13 (12.6)	
Platelet $<350 \times 10^9$/L	2449 (79.1)	2371 (79.2)	78 (75.7)	.388
$\geqslant 350 \times 10^9$/L	646 (20.9)	621 (20.8)	25 (24.3)	
Albumin <3.5 g/dL	1261 (40.7)	1212 (40.5)	49 (47.6)	.151
⩾3.5 g/dL	1834 (59.3)	1780 (59.5)	54 (52.4)	
CEA ⩽6 ng/mL	1410 (45.6)	1358 (45.4)	52 (56.3)	.129
>6 ng/mL	687 (22.2)	652 (21.8)	35 (28.2)	

Table 1 – (continued)

Characteristic	No. of patients (%)			P
	All (N = 3095)	non-VTE (N = 2992)	VTE (N = 103)	
Unknown	998 (32.2)	982 (32.8)	16 (15.5)	
CA19-9 ⩽37 U/mL	1281 (41.4)	1252 (41.8)	29 (28.2)	<.001
>37 U/mL	775 (25)	717 (24)	58 (56.3)	
Unknown	1039 (33.6)	1023 (34.2)	16 (15.5)	
CA72-4 ⩽4 U/mL	946 (30.6)	918 (30.7)	28 (27.2)	.019
>4 U/mL	1075 (34.7)	1021 (34.1)	54 (52.4)	
Unknown	1074 (34.7)	1053 (35.2)	21 (20.4)	

CEA, Carcinoembryonic antigen; VTE, venous thromboembolism; ECOG PS, Eastern Collaborative Oncology Group performance status; LN, lymph nodes; WBC, white blood cells.

identified incidentally on chemotherapy-specific follow-up imaging.

Nine of the 64 patients (14.5%, 95% CI, 5.5–23.5%) who could be followed-up died due to VTE. Of all VTE events, 61.1% occurred within 6 months after AGC diagnosis. Characteristics of patients with VTE are summarised in Table 2.

3.3. *Survival analysis*

The 1-year OS rate for the entire cohort was 45% (median OS, 10.67 months, 95% CI, 10.23–11.1 months). Univariate analysis showed that OS rates were significantly lower for patients with than without VTE (1-year OS, 40% versus 45.3%; 2-year OS, 10.5% versus 19.3%; HR, 1.23; 95% CI, 1.0–1.52; $P = 0.048$) (Fig. 1).

Univariate analysis showed that OS was also adversely affected by patient age (⩾65 years), Eastern Collaborative Oncology Group performance status (ECOG PS) (⩾2), tumour histology (poorly differentiated adenocarcinoma and signet ring cell carcinoma) and number of metastatic sites (⩾2). Multivariate analysis showed that significant factors independently affecting OS were age (⩾65 years, HR, 1.14; 95% CI, 1.04–1.26), ECOG performance status (⩾2, HR, 1.59; 95% CI, 1.43–1.76), tumour histology (poor differentiated adenocarcinoma and signet ring cell carcinoma, HR, 1.3; 95% CI, 1.19–1.49) and number of metastatic sites (⩾2, HR, 1.5; 95% CI, 1.37–1.66). By the multivariate analysis VTE was not an independent factor affecting OS ($P = 0.82$) (Table 3).

Among the patients with VTE, those who had VTE at the time of AGC diagnosis had poorer median OS than patients who had VTE after AGC diagnosis (4.5 months versus 10.7 months; HR, 2.171; 95% CI 1.2–3.93; $P = 0.009$) (Fig. 2). In all patients, the presence of VTE at the time of AGC diagnosis was an independent risk factor affecting survival, along with age, ECOG performance status, histology and number of metastatic sites, in multivariate analysis (HR, 1.91; 95% CI, 1.1–3.31, $P = 0.021$). The median time from VTE development to death was 2.6 months (95% CI, 1.4–3.8 months). Nine patients (8.7%) died due to VTE.

3.4. *Risk factors for development of VTE*

Several individual factors were significantly associated with VTE development in patients with AGC (Tables 4 and 5). Multivariate analysis showed that gender (female versus male, HR, 2.3; 95% CI, 1.4–4), primary tumour site in the stomach (cardia or fundus versus body or antrum, HR, 2.1; 95% CI, 1.2–4), number of metastatic sites (⩾2, HR, 5.6; 95% CI, 3–10.5), lung metastasis (HR, 4.4; 95% CI, 2.2–8.9) and increased baseline CA19-9 level (HR, 2.4; 95% CI, 1.4–4.3) were independent risk factors for VTE.

4. Discussion

We evaluated the incidence and predictors of VTE in patients with inoperable AGC treated with systemic chemotherapy. VTE presenting clinically as DVT and/or PE developed in 103 of the 3095 patients with AGC, with an overall incidence rate of VTE of 1.88 events/100 person-years and the 1-year cumulative incidences of 3.5%. This incidence was lower than the recently reported incidence of 13.3% in patients with stage IV stomach cancer.[18] Also, a previous study reported that the incidence of VTE was 13.6% with advanced gastroesophageal cancer experienced thromboembolic events, including arterial thrombosis, before and during chemotherapy.[19] Moreover, another recent study of specific combination chemotherapy regimens in AGC patients reported that the actuarial incidence of VTE was 10.1%.[20] It is difficult to directly compare our results with those of these previous studies due to differences in study populations and definitions of embolic events. Nevertheless, we observed a lower incidence rate of VTE in Korean than seen in previous studies of Western patients with AGC.

Race or ethnicity may play an important role in these differences. Asian-Pacific patients with several types of cancer, including AGC, were found to have a significantly lower risk of developing VTE than Caucasians,[5] and studies on general populations found that the incidence of VTE in Asian-Pacific patients was approximately five-fold lower than in Caucasians.[21–23] The relatively low incidence of VTE in Asians may be due to a low prevalence of genetic factors predisposing to VTE, including factor V Leiden.[24,25] Our patient population was at particularly high risk of developing VTE because they all had inoperable AGC and most were receiving chemotherapy. Nevertheless, the lower incidence of VTE in our study supports the hypothesis that the incidence of VTE is low among individuals of Asian ethnicity.

The occurrence of VTE has been found to have a significant adverse effect on survival.[5,7,16,26] Multivariate analysis of current study, however, showed that VTE did not significantly

Table 2 – Characteristics of patients with venous thromboembolism (VTE).

	No. of VTE patients (*N* = 103)	%
Type of VTE		
DVT	68	66
PE	46	44.7
DVT + PE	18	17.5
Upper extremities DVT	7	6.8
Comorbidities		
Yes	45	43.7
Hypertension & cardiovascular diseases	25	24.3
Diabetes	8	7.8
Pulmonary diseases	5	4.9
Liver diseases	3	2.9
Previous cancer history	8	7.8
Previous embolic history	3	2.9
No	58	56.3
Symptoms of VTE		
Yes	74	71.8
No (incidental)	29	28.2
Synchronous VTE with advanced gastric cancer (AGC) at diagnosis		
Yes	15	14.6
No	88	85.4
Palliative chemotherapy		
Yes	93	90.3
No	10	9.7
Type of chemotherapy before VTE		
Fluorouracil	79	76.7
Cisplatin	79	76.7
Taxanes	43	41.7
Irinotecan	19	18.3
Oxaliplatin	15	14.6
Cetuximab	3	2.9
Bevacizumab	5	4.9
D-dimer – median (range) (normal range < 0.5 μm/mL)	11 (0.95–97.3 μm/mL)	
Elevated D-dimer	64	62.1
Non-elevated D-dimer	0	0
Unknown	39	37.9
Treatment		
Yes	85	82.5
Aspirin	1	1
Heparin	5	4.9
Low-molecular-weight heparin (LMWH)	20	19.4
Heparin + warfarin	12	11.7
LMWH + warfarin	34	33
Warfarin	9	8.7
Vena cava filters	4	3.9
No	18	17.5
Death		
Due to VTE	9	8.7
Due to disease progression	53	51.5
Unknown	41	39.8

DVT, deep vein thrombosis; PE, pulmonary thromboembolism.

affect OS, after adjusting for age, ECOG performance status and tumour histology ($P = 0.82$). A diagnosis of VTE may reflect more serious underlying medical conditions. Patients with VTE may have more aggressive tumour biology and/or more serious underlying medical illnesses. On the other hand, owing to the short survival of patients with advanced-stage disease, VTE may have a much reduced impact. Therefore, VTE itself is not independently associated with survival and maybe it reflects a more advanced or more aggressive cancer.

We identified several risk factors related to VTE development. Other, previously identified risk factors, including

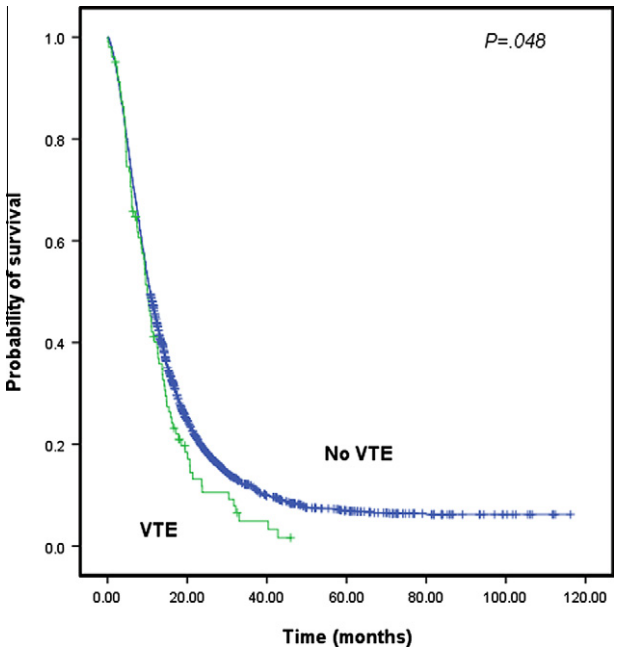

Fig. 1 – Kaplan–Meier survival curve for AGC patients with or without venous thromboembolism (VTE).

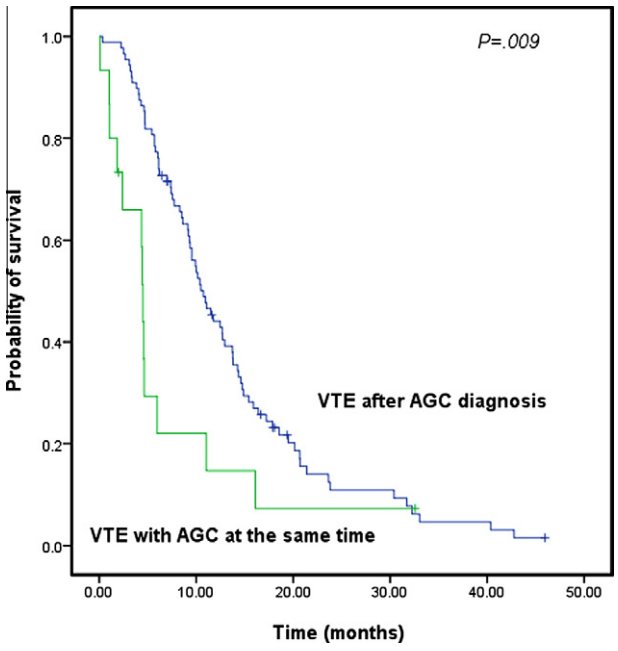

Fig. 2 – Kaplan–Meier survival curves of patients with VTE simultaneously diagnosed with AGC and those with VTE detected after AGC diagnosis.

advanced age, reduced performance status and surgery,[27] were not significant predictors of VTE development on multivariate analysis. Because all the patients of current study received chemotherapy, elderly patients and those with reduced performance status not suitable for chemotherapy may have been excluded. Previous studies have shown no significant difference in VTE rates between men and women.[28,29] However, men with cancer hospitalised for neutropenia were more likely than women to have arterial thrombotic events, whereas, in the subgroup over 65 years of age, women were more likely to have venous events than men.[12] Another retrospective study supports the overall increased risk of VTE in female cancer patients (OR, 1.1; $P < 0.0001$).[1] Also, the patients with proximal gastric cancer had more chance of VTE in our study. However, the exact reason for that is unclear. It has been speculated that gastroesophageal junctional cancer has been linked to obesity, acid reflux disease, smoking and alcohol ingestion. Obesity and smoking are also risk factors for VTE development.[2] This study did not investigate these risk factors in detail, but the high recent incidence of proximal gastric cancer maybe reflects an increasing adoption of Western lifestyles among Asian populations. Interestingly, we found that the risk of VTE was significantly higher among patients with than without lung metastasis. Patients with gastrointestinal or lung cancer are at high risk of VTE.[30] Patients with lung cancer and metastases to the liver and brain were shown to have higher rates of VTE than lung cancer patients with other sites of metastases.[31] No previous study has reported, however, that lung metastasis is associated with VTE in gastric cancer patients. Regular chest CT scans in patients with lung metastases may be associated with an increased probability of finding asymptomatic VTE.

In previous phase III studies,[14,20,32] VTE was reported as adverse events of each chemotherapy regimens for the treatment of AGC. There was significant lower incidence of thromboembolism in the oxaliplatin group than cisplatin group,

Table 3 – Multivariate analysis of risk factors for mortality (Cox regression) in patients with advanced gastric cancer (AGC).

Variable	Hazard ratio	95% confidence interval	*P*
Age (<65 versus ⩾65 years)	1.14	1.04–1.26	.008
Eastern Collaborative Oncology Group PS (1 versus ⩾2)	1.59	1.43–1.76	<.001
Histology (well/moderately differentiated versus poorly differentiated/signet ring cell)	1.31	1.19–1.44	<.001
Number of metastatic sites (1 versus ⩾2)	1.51	1.37–1.66	<.001
VTE (no versus yes)	1.03	0.83–1.28	.821
VTE concurrently diagnosed AGC (no versus yes)	1.91	1.1–3.31	.021

PS, performance status; VTE, venous thromboembolism.

Table 4 – Univariate analysis of variables associated with development of venous thromboembolism (VTE).

Variable	Hazard ratio	95% confidence interval	P
Age (<65 versus ⩾65 years)	1.12	0.72–1.72	.623
Gender (M versus F)	1.66	1.12–2.46	.012
Eastern Collaborative Oncology Group performance status (1 versus ⩾2)	1.22	0.79–1.9	.373
Primary tumour site on stomach (N = 2236 (72.2%))[a] (antrum/body versus cardia/fundus)	2.44	1.46–4.06	.001
Disease status (recurrent versus initially metastatic)	1.03	0.68–1.57	.885
Previous surgery history (no versus yes)	1.07	0.72–1.58	.745
Histology (N = 2415(78.1%))[a] (well/moderately differentiated versus poorly differentiated/signet ring cell carcinoma)	1.15	0.73–1.80	.548
Measurable disease (yes versus no)	1.26	0.85–1.87	.25
Number of metastatic site (1 versus ⩾2)	10.38	6.38–16.87	<.001
Liver (no versus yes)	1.39	0.94–2.05	.104
Peritoneum (no versus yes)	1.26	0.81–1.94	.309
Lung (no versus yes)	9.75	6.14–15.48	<.001
Bone (no versus yes)	3.01	1.73–5.25	<.001
Number of palliative chemotherapy (1 versus ⩾2)	1.59	1.04–2.42	.031
Baseline laboratory parameters			
CEA (non-elevated versus elevated)[b] (N = 2097 (67.8%))[a]	1.4	0.9–2.17	.131
CA19-9 (non-elevated versus elevated)[b] (N = 2056 (66.4%))[a]	3.49	2.22–5.5	<.001
CA72-4 (non-elevated versus elevated)[b] (N = 2021 (65.3%))[a]	1.73	1.09–2.76	.02
Haemoglobin (⩽10 g/dL versus >10 g/dL)	0.84	0.53–1.33	.463
White blood cells (WBC) (⩽11×10^9/L versus >11×10^9/L)	1.86	1.02–3.38	.043
Platelet (<350×10^9/L versus ⩾350×10^9/L)	1.22	0.77–1.94	.389
Albumin (<3.5 g/dL versus ⩾3.5 g/dL)	0.75	0.51–1.11	.153

[a] Patients who could be assessed.
[b] Normal range of CEA ⩽6 ng/mL, CA19-9 ⩽37 U/mL, CA72-4 ⩽4 U/mL. CAE, Carcinoembryonic antigen.

Table 5 – Multivariate analysis of variables associated with development of venous thromboembolism (VTE).

Variable	Hazard ratio	95% confidence interval	P
Gender (male versus female)	2.32	1.35–3.97	.002
Primary tumour site on stomach (antrum/body versus cardia/fundus)	2.12	1.17–4.05	.019
Number of metastatic site (1 versus ⩾2)	5.58	2.96–10.52	<.001
Number of palliative chemotherapy (1 versus ⩾2)	1.45	0.84–2.51	.187
Lung metastasis (no versus yes)	4.43	2.2–8.92	<.001
Bone metastasis (no versus yes)	1.17	0.5–2.74	.717
CA19-9 (non-elevated versus elevated)	2.42	1.36–4.30	.003
CA72-4 (non-elevated versus elevated)	1.09	0.6–1.99	.779
White blood cells (WBC) (⩽11×10^9/L versus >11×10^9/L)	1.04	0.42–2.58	.933

driven by the significant difference in venous events (7.6% versus 15.1%, $P < 0.001$).[14,20] In this study, we did not directly compare to several chemotherapy regimens for the development of VTE. However, in Korea, FP or capecitabine plus cisplatin are most widely used as first-line chemotherapy for AGC treatment. Among the 103 patients diagnosed with VTE, 93 (90.3%) had received more than one cycle of chemotherapy, with 79 (76.7%) receiving fluorouracil and cisplatin-containing chemotherapy before VTE development. Thromboembolic complications of chemotherapy sometimes lead to morbidity and mortality. The choice of cytotoxic regimen should be considered according to risk and benefit assessment.

We analysed a large cohort of relatively homogeneous patients, almost all of whom were treated with systemic chemotherapy, including fluoropyrimidine and cisplatin, for

metastatic or recurrent AGC. All of our data, including OS, were collected prospectively. The limitation of our study was that the clinical identification of VTE was performed retrospectively. Indeed, we included only those patients with radiologically confirmed VTE and we therefore may have excluded patients with clinically probable or possible VTE, resulting in a possible underestimation of VTE rates. The low incidence of VTE we observed may also have been due to selection bias. Our cohort selection included registered patients with AGC who were able to tolerate chemotherapy, thus possibly excluded patients who had already experienced a severe VTE or PE before starting chemotherapy.

In conclusion, this large population-based cohort study of patients with inoperable AGC who were receiving chemotherapy confirmed the incidence rate of VTE. Our findings indicate that patient survival may not be adversely affected by the new development of VTE during chemotherapy for metastatic or recurrent AGC. Female gender, primary site in the upper portion of the stomach, two or more metastatic sites, lung metastasis and increased baseline CA19-9 level were strong predictors of VTE. Further prospectively designed assessments are warranted to validate our findings.

Conflict of interest statement

None declared.

Acknowledgement

The authors made no disclosures.

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