ORIGINAL RESEARCH

Outcome of Thromboembolic Events and Its Influence on Survival Time of Advanced NSCLC Patients Treated with Antiangiogenic Therapy

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Background: Antiangiogenetic therapy and lung cancer, per se, are associated with an increased risk of thromboembolic events (TE). We aim to evaluate the pattern and outcome of TE as well as its influence on survival time of advanced non-small cell lung cancer (NSCLC) patients receiving antiangiogenic therapy.

Methods: This was a retrospective cohort study, which included advanced NSCLC patients receiving antiangiogenic therapy. All TE were confirmed by objective image studies. We disclosed the presentation and risk factors of TE and evaluated its influence on outcome.

Results: A total of 427 patients were included. TE occurred in 43 patients (10.1%). Deep vein thrombosis (DVT) was the most common TE (n = 20). Up to 46.2% of DVT did not occur in the typical lower extremities. Two patients died of TE. Among patients with continuous use or reuse of antiangiogenetic therapy, 18.2% had recurrent TE events. At the occurrence of TE, 28 patients experienced progressive disease (TE with PD), while tumor status remained stable in another 15 patients (TE without PD). The post-TE survival of patients without and with PD were 8.9 months (95% CI 3.9–13.9) vs 2.2 months (95% CI 0.1–4.3), P = 0.012. As compared with patients without TE (31.4 months [95% CI 27.1–35.7]), TE with PD patients experienced a significantly shorter overall survival (20.1 months [95% CI 15.5–24.6]), but TE without PD patients had comparable survival time (32.7 months [95% CI 7.4–28.1]) (P = 0006). The use of hormone analogue and proteinuria predicted the events among TE with PD group (aOR 2.79 [95% CI 1.13=6.92]; P = 0.027) and TE without PD group (aOR 4.30 [95% CI 1.13–16.42]; P = 0.033), respectively.

Conclusion: Owing to the different risk factors and influences on the survival time, TE with and without PD may be two different disease entities.

Keywords: non-small cell lung cancer, NSCLC, antiangiogenesis, bevacizumab, ramucirumab, thromboembolism

Introduction

Lung cancer is the leading cause of cancer-related death worldwide.[1] Owing to advances in the molecular pathogenesis of the disease and the availability of new treatment options, the outcome of non-small cell lung cancer (NSCLC) has improved substantially.[2] Antiangiogenic therapy, which can disrupt the blood supply to tumors and crosstalk with other antineoplastic treatments, have been proven with clinical benefits for patients with advanced NSCLC.[3,4]

1251

Lung cancer cells and other malignancies can result in a hypercoagulable state through interaction with vascular endothelial cells, production of procoagulants, and enhancement of platelet-aggregating activities.[5–7] Based on the MEGA study, lung cancer is associated with a 22-fold increase in the risk of thromboembolic events (TE) as compared with subjects without malignancy.[8]

In addition to lung cancer per se, the use of antiangiogenic therapy is associated with an increased risk of developing TE. Both vascular endothelial growth factor (VEGF) ligand and its receptor are druggable targets for anticancer therapy with antiangiogenic activity. Bevacizumab and ramucirumab have been approved to treat advanced NSCLC.[9] However, the treatment outcome and risk factors of TE as well as its influence on the survival time of NSCLC patients treated with antiangiogenic therapy remain unclear. Moreover, we speculate that TE in subjects whose tumors are remaining controlled may be different from that in patients who experience disease progression. Herein, we conducted this study to address this issue.

Patients and Methods

Patients

This was a retrospective study and we analyzed lung cancer patients diagnosed and treated at Taichung Veterans General Hospital from March 2013 to May 2021. To be eligible for the study, patients were required to have cytologically or pathologically confirmed NSCLC, inoperable stage III to IVB disease, history of antiangiogenic therapy, including bevacizumab or ramucirumab, and precise survival follow-up data. Patients were excluded if they had mixed components of small cell carcinoma, TE before antiangiogenic therapy, stage III disease with an attempt of curative local therapy, other active malignancy, or incomplete data records.

Data Records for Analysis

Clinical data for analysis included patients' age, gender, smoking status, the Eastern Cooperative Oncology Group performance status (ECOG PS), histological type, driver mutation status, tumor stage, antiangiogenic agents, combination regimen, concomitant medications of interest, treatment lines, underlying comorbidities, adverse events of antiangiogenic therapy, TE, tumor control status at the time of TE occurrence, and survival follow-up data. Lung cancer TNM (tumor, node, and metastases) staging was conducted according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.[10] All TE were diagnosed based on objective imaging studies, such as angiography, computed tomography, or magnetic resonance imaging. The spectrum of TE, treatments, and outcomes was recorded. One-dimensional measurements as determined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used in this study to evaluate the status and response of lung cancer treatment.[11]

The study was performed in accordance with the ethical standards described in the Declaration of Helsinki and was approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB No. CF12019 and CF20175). Written informed consent for clinical data records and genetic testing was obtained from all patients.

Driver Mutation Analysis

Six oncogenic drivers, including *EGFR, Kirsten rat sarcoma viral oncogene homolog* (*KRAS), v-raf murine sarcoma viral oncogene homolog B* (*BRAF), human epidermal growth factor receptor 2* (*HER2), ALK*, and *ROS1* were tested. *EGFR, KRAS, BRAF*, and *HER2* mutations were assessed using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). DNA was extracted from the tumors using a QIAmp DNA Mini kit (Qiagen, Valencia, CA) following the manufacturer's protocol. We performed the analysis according to the manufacturer's protocol for the MassARRAY system (Sequenom, San Diego, CA). In the biochemical reaction, a polymerase chain reaction, followed by single nucleotide extension, was performed using primers and corresponding detection probes to amplify the regions containing each target mutation. After SpectroClean Resin clean up, samples were loaded onto the matrix of SpectroCHIP by Nanodispenser (Matrix) and then analyzed using Bruker Autoflex MALDI-TOF MS. Data were collected and analyzed with Type 4 software (Sequenom). *ALK* fusion mutation was tested with a fully automated IHC assay (Ventana IHC, Ventana, Tucson, AZ) using the pre-diluted Ventana anti-ALK (D5F3) Rabbit monoclonal

primary antibody and *ROS1* fusion mutation was determined by fluorescent in situ hybridization (FISH) as previously described.[12]

Statistical Methods

Univariate analyses of the association between TE and patients' characteristics were performed using the Fisher's exact test and independent *t*-test. The Kaplan–Meier method was used to estimate the survival time. Differences in survival time were analyzed by the Log rank test. The logistic regression model and Cox proportional hazard model were used for multivariate analyses of the risk factors of TE and survival outcomes. All statistical tests were carried out using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Two-tailed tests and P values <0.05 for significance were implemented.

Results

Patients and Their Demographic Data

From March 2013 to May 2021, a total of 457 patients who met the inclusion criteria were identified. The patient selection flowchart is shown in Figure 1. Thirty patients were excluded because of mixed small cell carcinoma histology, TE before antiangiogenic therapy, stage III with an attempt of curative local therapy, and incomplete data records. Finally, 427 patients were included for analysis. Patients' characteristics and demographic data are summarized in Table 1. The median age was 59 years. Among the patients, 217 patients (50.8%) were female, 290 patients (67.9%) were non-smokers, and 302 (70.7%) had ECOG PS 0–1. Adenocarcinoma accounted for the most common histological type (96.5%), and *EGFR* was the most common driver mutation (59.5%). Cancer stage in up to 72.1% of patients was stage IVB, and 298 patients (69.8%) had comorbidities other than lung cancer.
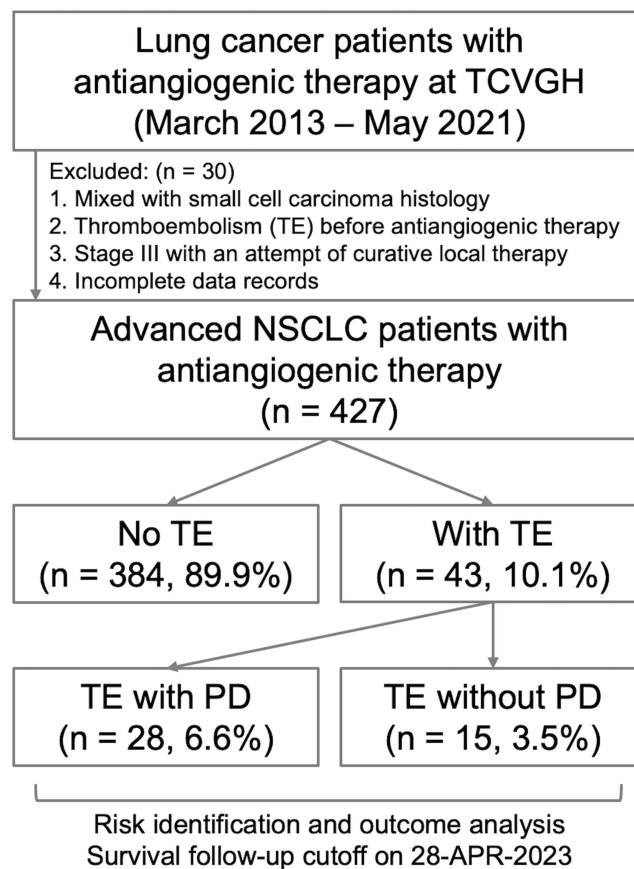
Figure 1 Patient selection and analysis flowchart.
Abbreviations: TCVGH, Taichung Veterans General Hospital; NSCLC, non-small cell lung cancer; TE, thromboembolic event; PD, progressive disease.

Table 1 Patients' Characteristics and Demographic Data

Characteristics	N = 427
Age, years, median (range)	59 (26–85)
Gender, n (%)	
Female	217 (50.8)
Male	210 (49.2)
Smoking status, n (%)	
Non-smokers	290 (67.9)
Smokers	137 (32.1)
ECOG PS, n (%)	
0–1	302 (70.7)
2 or more	125 (29.3)
Histology, n (%)	
Adenocarcinoma	412 (96.5)
Non-adenocarcinoma[1]	15 (3.5)
Driver mutation, n (%)	
EGFR	254 (59.5)
KRAS	19 (4.4)
ALK	14 (3.3)
HER2	9 (2.1)
BRAF	3 (0.7)
ROS1	2 (0.5)
Others[2]	3 (0.7)
Unfound/unknown	123 (28.8)
Tumor stage, n (%)	
Inoperable stage IIIB/C	7 (1.6)
Stage IVA	112 (26.2)
Stage IVB	308 (72.1)
Antiangiogenic therapy, n (%)	
Bevacizumab	345 (80.8)
Ramucirumab	24 (5.6)
Bevacizumab and ramucirumab	58 (13.6)
Combination regimen, n (%)	
Chemotherapy	274 (64.2)
Targeted therapy[3]	129 (30.2)
Others[4]	24 (5.6)
Treatment lines, n (%)	
First or second line	275 (64.4)
Third line or later	152 (35.6)
Other underlying comorbidities, n (%)	
Yes[5]	298 (69.8)
No	129 (30.2)

Notes: [1]Includes 8 squamous cell carcinoma (all of them with ramucirumab therapy), 3 not otherwise specified (NOS) carcinoma, 2 adenosquamous cell carcinoma, 1 lymphoepithelioma-like carcinoma, and 1 adenocarcinoma mixed with large cell neuroendocrine carcinoma. [2]Includes 3 with mixed *EGFR* & other mutation(s). [3]Includes 4 with *ALK* inhibitors; otherwise with EGFR-TKI. [4]Includes 16 with chemotherapy plus immunotherapy, 6 with chemotherapy plus targeted therapy, and 2 with immunotherapy. [5]Most common underlying comorbidities were chronic kidney disease, hypertension, and diabetes mellitus.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine, kinase inhibitor.

In the case of antiangiogenic therapy, 80.8% and 5.6% of patients received bevacizumab and ramucirumab, respectively, while 13.6% had previously received both. Antiangiogenic therapy was prescribed in the first or second line setting in 64.4% of our population and was combined with chemotherapy and targeted therapy in 64.2% and 30.2% of subjects, respectively.

There were 43 patients (10.1%) with TE in our population. The tumor control status at the time of TE occurrence were progressive disease (PD) in 28 patients (TE with PD group, 6.6%) and were remaining stable in 15 patients (TE without PD group, 3.5%).

The Pattern, Treatment, and Outcome of Thromboembolic Events

The spectrum of TE and the outcome of TE management are summarized in Figure 2. The most common type of TE was deep vein thrombosis (DVT) (n = 20, 46.5%), followed by pulmonary embolism (n = 14, 32.6%), and combined PE and DVT (n = 6, 14.0%). Three patients (7.0%) had cerebral vascular accidents (2 with middle cerebral artery infarction and 1 with multiple embolic strokes). Although the most common site of DVT was typically in the lower limbs (n =14, 53.8%), up to 46.2% of DVT occurred in other uncommon locations, which included the subclavian vein, jugular vein, brachiocephalic vein, axillary vein, and more distal veins in the upper limbs.

Most of the patients had undergone anticoagulants (n = 40). Two patients received antiplatelet agents because of the cerebrovascular accident. The most common initial anticoagulant regimen was lower molecular weight heparin (LMWH) (n = 36), while four patients received non-vitamin K antagonist oral anticoagulant (NOAC) therapy. One patient did not receive any treatment for TE because of the small size of thrombosis in the pulmonary artery and there were no significant clinical symptoms. Two patients (4.7%) died of TE, which presented with massive middle cerebral artery territory infarction.

Most of the patients stopped the antiangiogenic therapy after documentation of TE; five patients were maintained on the treatment and six patients were rechallenged with antiangiogenic therapy after clinical stabilization. TE recurred in one patient who was kept on the treatment and in another patient who was rechallenged.
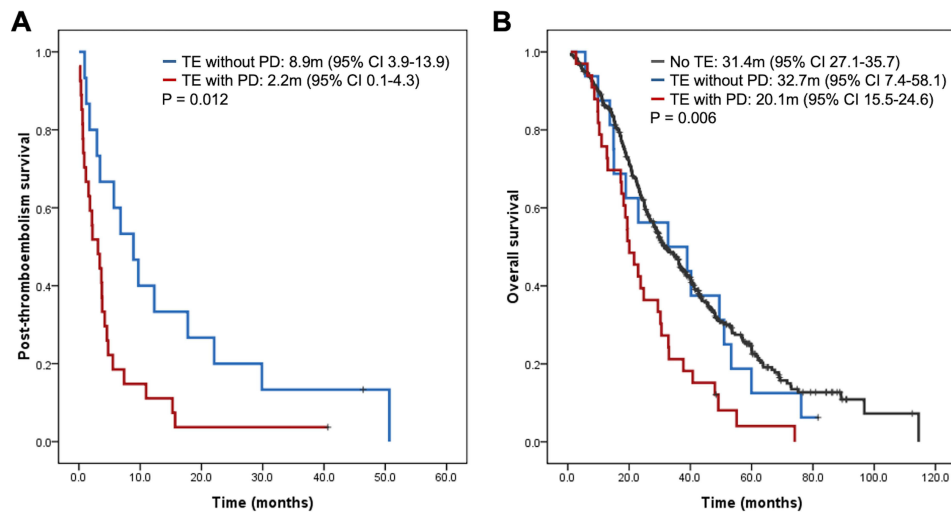
Impact of Thromboembolic Events on Patients' Survival Time

In the present study, we assessed the post-thromboembolism survival and overall survival (OS) as the primary outcome parameters. The OS was defined as the duration from documented inoperable advanced stage to death of any cause. In the
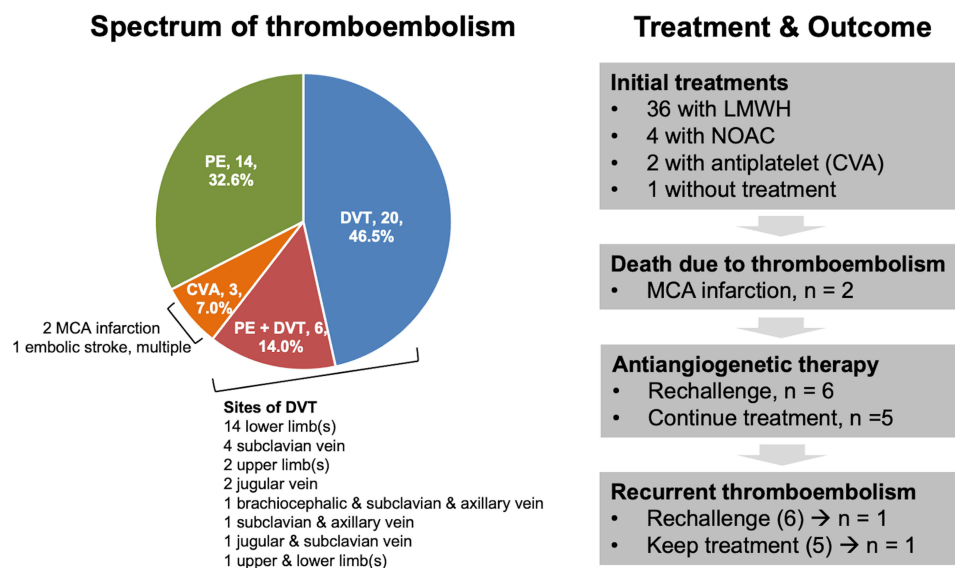
Figure 2 Pattern, treatment, and outcome of thromboembolic events.
Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; CVA, cerebrovascular accident; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist oral anticoagulant; MCA, middle cerebral artery.

Figure 3 Impact of thromboembolic events (TE) and disease control status at the time of TE on the survival time: post-thromboembolism survival (**A**) and overall survival (**B**). **Abbreviation**: PD, progressive disease.

overall population, patients with TE experienced a significantly shorter OS as compared with patients without TE (22.9 months [95% CI 16.1–29.7] vs 31.4 months [95% CI 27.1–35.7], P = 0.008). Among patients with TE, the median post-thromboembolism survival was 3.7 months (95% CI 2.8–4.6).

Although both lung cancer, per se, as well the antiangiogenic therapy would increase the risk of TE, we supposed that TE in subjects whose tumors were remaining controlled may be different from that in patients who experienced disease progression. We further evaluated the influence of tumor control status at the time of TE on patients' survival time. The results are shown in Figure 3. Patients in the TE with PD group experienced a significantly shorter post-thromboembolic survival than those in the TE without PD group (2.2 months [95% CI 0.1–4.3] vs 8.9 months [95% CI 3.9–13.9], P = 0.012) (Figure 3A). There was no significant difference in the overall survival between patients without TE and those in the TE without PD group (31.4 months [95% CI 27.1–35.7] vs 32.7 months [95% CI 7.4–58.1]). By contrast, patients in the TE with PD group had a significantly shorter overall survival (20.1 months [95% CI 15.5–24.6], P = 0.006) (Figure 3B).

In the multivariate analysis shown in Table 2, tumor control status at the time of TE occurrence independently predicted the overall survival. As compared with patients without TE, TE with PD group was associated with a significantly higher mortality risk (aHR 1.55 [95% CI 1.03–2.34], P = 0.036), but TE without PD group had a comparable outcome (aHR 1.17 [95% CI 0.68–2.02], P = 0.575).

Additionally, baseline ECOG PS (2 or more) were independently associated with a worse outcome (aHR 2.10 [95% 1.58–2.79], P < 0.001 in the TE without PD group and 2.06 [95% CI 1.58–2.68], P < 0.001 in the TE with PD group, respectively).

Risk Factors of Thromboembolic Events

We further analyzed the risk factors of TE among TE with PD and without PD groups; the results are summarized in Table 3. In the TE with PD group, only the use of the hormone therapy—specifically, synthetic progesterone as an

Table 2 Multivariate Analysis of the Impact of Thromboembolic (TE) Events on Overall Survival

Patients	OS, months (95% CI)	HR (95% CI)	P value[1]	aHR[2] (95% CI)	P value[1]
No TE	31.4 (27.1–35.7)	1.00 (reference)		1.00 (reference)	
TE without PD	32.7 (7.4–58.1)	1.19 (0.69–2.04)	0.529	1.17 (0.68–2.02)	0.575
TE with PD	20.1 (15.5–24.6)	1.87 (1.26–2.78)	0.002	1.55 (1.03–2.34)	0.036

Notes: [1]By Cox proportional hazard model. [2]Adjusted by age, gender, smoking status, ECOG PS, histology, driver mutations, tumor stage, BMI, comorbidities, usage of hormones, and treatment regimens.
Abbreviations: TE, thromboembolic events; PD, progressive disease; OS, overall survival; HR, hazard ratio.

appetite-enhancing agent, and the numbers of cycles of antiangiogenic therapy were significantly associated with the occurrence of TE. Of note, more patients had undergone hormone treatment in patients with TE than those without events (75.0% vs 53.1%, P = 0.030). Patients of the TE with PD group also tended to receive fewer cycles of antiangiogenic therapy than those without TE (6.6 ± 6.8 vs 10.5 ± 10.8, P = 0.008). In the case of adverse events related to antiangiogenic therapy, a total of 118 patients (27.6%) developed hypertension, including Grade 1, 2, and 3 in 74, 39,

Table 3 Univariate Analysis of Patients' Characteristics and Thromboembolic Events (TE)

Factor	No TE	TE without PD	P value[2]	TE with PD	P value[2]
Age, n (%)			0.446		0.782
< 70 years	332 (86.5)	12 (80.0)		24 (85.7)	
≥ 70 years	52 (13.5)	3 (20.0)		4 (14.3)	
Gender, n (%)			0.795		0.436
Female	198 (51.6)	7 (46.7)		12 (42.9)	
Male	186 (48.4)	8 (53.3)		16 (57.1)	
Smoking, n (%)			0.573		0.676
Non-smokers	263 (68.5)	9 (60.0)		18 (64.3)	
Smokers	121 (31.5)	6 (40.0)		10 (35.7)	
ECOG PS, n (%)			0.249		0.523
0–1	271 (70.6)	13 (86.7)		18 (64.3)	
2 or more	113 (29.4)	2 (13.3)		10 (35.7)	
Histology, n (%)			0.397		0.245
Adenocarcinoma	372 (96.9)	14 (93.3)		26 (92.9)	
Non-adenocarcinoma	12 (3.1)	1 (6.7)		2 (7.1)	
Driver mutation, n (%)			0.378		0.196
Yes	278 (72.4)	9 (60.0)		17 (60.7)	
No	106 (27.6)	6 (40.0)		11 (39.3)	
Tumor stage, n (%)			0.144		0.378
Stage III–IVA	107 (27.9)	7 (46.7)		5 (17.9)	
Stage IVB	277 (72.1)	8 (53.3)		23 (82.1)	
Body mass index, n (%)			1.000		0.843
< 24	237 (61.7)	9 (60.0)		18 (64.3)	
≥ 24	147 (38.3)	6 (40.0)		10 (35.7)	
Comorbidities, n (%)			1.000		1.000
Yes	267 (69.5)	11 (73.3)		20 (71.4)	
No	117 (30.5)	4 (26.7)		8 (28.6)	
Hormones, n (%)[1]			0.186		0.030
Yes	204 (53.1)	11 (73.3)		21 (75.0)	
No	180 (46.9)	4 (26.7)		7 (25.0)	
Antiplatelet therapy, n (%)			1.000		0.654
Yes	20 (5.2)	0 (0.0)		2 (7.1%)	
No	364 (94.8)	15 (100.0)		26 (92.9)	
Antiangiogenesis, n (%)			0.174		0.388
Bevacizumab	314 (81.8)	10 (66.7)		21 (75.0)	
Ramucirumab	22 (5.7)	1 (6.7)		1 (3.6)	
Both	48 (12.5)	4 (26.7)		6 (21.4)	

(Continued)

Table 3 (Continued).

Factor	No TE	TE without PD	P value[2]	TE with PD	P value[2]
Treatment cycles	10.5±10.8	10.2±10.0	0.913	6.6±6.8	0.008
Combination regimen, n (%)			1.000		0.277
Chemotherapy	243 (63.3)	10 (66.7)		21 (75.0)	
Targeted therapy	119 (31.0)	5 (33.3)		5 (17.9)	
Others	22 (5.7)	0 (0.0)		2 (7.1)	
Treatment lines, n (%)			0.591		0.229
First or second line	249 (64.8)	11 (73.3)		15 (53.4)	
Third line or later	135 (35.2)	4 (26.7)		13 (46.4)	
Proteinuria AE, n (%)			0.033		0.328
Yes	194 (50.5)	12 (80.0)		11 (39.3)	
No	190 (49.5)	3 (20.0)		17 (60.7)	
Hypertension AE, n (%)			1.000		0.279
Yes	109 (28.4)	4 (26.7)		5 (17.9)	
No	275 (71.6)	11 (73.3)		23 (82.1)	

Notes: [1]Indicates synthetic progesterone as an appetite-enhancing agents. [2]Compared with patients without TE: by independent *t*-test for treatment cycles and otherwise by Fisher's exact test.
Abbreviations: TE, thromboembolism; PD, progressive disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AE, adverse events.

and 5 subjects, respectively, and a total of 217 patients (50.8%) had proteinuria, including Grade 1, 2, and 3 in 107, 106, and 4 subjects, respectively. However, there was no significant association between the adverse events and the occurrence of TE among TE with PD group. In the multivariate analysis, only the use of hormone therapy correlated with TE with PD independently (aOR 2.79 [95% CI 1.13–6.92], P = 0.027).

Regarding the TE without PD group, proteinuria was significantly associated with these events. More patients in the TE without PD group developed proteinuria than in those without TE (80.0% vs 50.5%, P = 0.033). In the multivariate analysis, proteinuria was the only factor that independently predicted TE occurrence (aOR 4.30 [95% CI 1.13–16.42], P = 0.033).

Neither the underlying comorbidities nor the sites of lung cancer metastasis correlated with the occurrence of TE with PD and TE without PD (Supplementary Tables 1 and 2).

Discussion

Antiangiogenic therapy is currently an important part of treatments for patients with advanced NSCLC.[13–15] Randomized control trials have demonstrated benefits of adding antiangiogenic therapy into standard chemotherapy, target therapy, or immunotherapy, which could prolong the survival time.[3,4,16] However, antiangiogenic therapy increases the risk of TE in cancer patients. In a meta-analysis by Nalluri et al, incidence rates of all-grade and high-grade TE among cancer patients receiving bevacizumab were 11.9% and 6.3%, respectively.[17] In the Phase 4 SAiL (MO19390) study evaluating the safety and efficacy of first-line bevacizumab-based therapy in advanced non-squamous NSCLC, approximately 8% of patients had grade 3 TE and 1% of patients died due to TE.[18] While it has been established that there exists an increased risk of TE caused by antiangiogenic therapy, these prior studies did not evaluate the risk factors of TE and its influence on patients' survival time. In the present study, TE occurred in 10.1% of our patients. We disclosed the pattern, treatment, and outcome of TE. Moreover, we analyzed its influence on patients' survival time and explored the possible risk factors of TE.

Regarding the spectrum of TE, most of our patients had venous TE, including pulmonary embolism and DVT. Of note, approximately half of the DVT events occurred at unusual sites, such as the upper extremities, and the subclavian, axillary, and jugular veins. Additionally, there were three patients with arterial TE. In a population-based study, DVT in

the upper extremities only accounts for 4.4% of all venous thromboses and 38% of these patients had underlying malignancies.[19] Previous studies have also revealed that approximately 10–50% of cancer-related DVT develop at unusual sites.[20,21]

Currently, LMWH and certain NOACs are the preferred treatments for cancer patients with TE.[22] Whenever the diagnosis is made and treatment is prescribed promptly, the outcome of TE is usually favorable. Most of our patients were treated with LWMH and NOAC initially, except for two patients with CVA. Only two of our patients died of TE, which presented with massive middle cerebral artery territory infarction. Another important issue is whether to cease antiangiogenic therapy when TE occurs, and it remains unclear whether the patient can undergo antiangiogenic therapy again when TE stabilizes. In our study, five patients were kept on antiangiogenic therapy after TE had occurred and six patients were rechallenged with antiangiogenic therapy. Two of them experienced recurrent TE. Since some patients may continue to benefit from antiangiogenic therapy, more studies are required in order to reach a consensus on the optimal treatment and follow-up plans for these patients.

In two comprehensive population-based studies, patients with malignancy had a 4- to 7-fold increase in the risk of venous thrombosis compared with subjects without malignancy.[6,7] Importantly, patients with distant metastasis had a higher risk of TE than those without metastasis, which implies that the more advanced malignancies are more likely to activate the cascade of cancer-induced thrombosis. Prior studies have suggested a two-way clinical association between TE and cancer. Cancer enhances the clotting activities through several mechanisms, such as production of procoagulant and fibrinolytic activities, expression of adhesion receptors, release of cytokines and angiogenic factors, direct blood-clotting activation, and activation of host-cell procoagulant and proadhesive cells. All these activities facilitate thrombin and fibrin formation and lead to a hypercoagulable state. Moreover, prothrombotic activities, such as tissue factors and VEGF, could induce cancer neovascularization, proliferation, and metastasis, and result in cancer progression.[5,23] Since most of our patients had metastatic disease, which is associated with a higher risk of TE, we speculated that not all of the TE were related to the antiangiogenic therapy. Herein, we supposed that TE in subjects whose tumors were remaining controlled may be different from that in patients who experienced disease progression. Therefore, we evaluated the influence of tumor control status at the time of TE on patients' survival time and suggested that its influence on patients' outcomes were different between the two groups of patients.

Antiangiogenic therapy-related TE had a dose-dependent relationship. Studies by Patel et al and Yu et al both suggested that higher cycles of bevacizumab treatment were associated with a higher risk of TE.[24,25] Herein, patients in the TE with PD group received significantly fewer cycles of antiangiogenic therapy, which implies that these patients might have had a more resistant disease and did not respond to antiangiogenic therapy well. In fact, these patients experienced a significantly shorter survival time. Taken together, these observations suggested that the TE in these patients were mainly a result of advanced lung cancer per se, rather than the antiangiogenic therapy. Hussain et al reported that patients with NSCLC treated with megestrol acetate as an appetite stimulant had a 3-fold increase in the risk of DVT compared to those without megestrol acetate.[26] Similar results were noted in patients among the TE with PD group, because use of this hormone was the only significant risk factor.

By contrast, TE without PD group had different risk factors and influences on the survival time. These patients received more cycles of antiangiogenic therapy than those among TE with PD group, which implies better treatment responses to antiangiogenic therapy. Although the TE occurred, their outcomes were similar to those without TE. The prevalence of TE was 3.5% in this group, which was lower compared with prior studies.[17,18,27] It may be that these studies did not classify TE according to the tumor control status. Moreover, proteinuria was an independent predictor of treatment-related TE. Previous studies have suggested a correlation between thrombosis and proteinuria, particularly for patients with nephrotic syndrome.[28,29] In nephrotic syndrome, primary damage to the glomerular membrane leads to leakage of albumin and coagulation regulatory proteins, and the resultant hypoalbuminemia increases hepatic synthesis of albumin and coagulation factors simultaneously, leading to a hypercoagulable state. In preclinical studies, inhibition of VEGF results in endothelial cell edema and detachment from the glomerular basement membrane, leading to the disruption of the filtration barrier.[30] A retrospective study by Sparks et al also suggested a trend of increasing TE in bevacizumab-treated patients with higher proteinuria.[31] The pathophysiology of antiangiogenic therapy-related

proteinuria is not fully understood. Further studies are still required to explore the pathophysiology and the relationship between TE and proteinuria.

In our study, there was no significant difference in the risk of TE between bevacizumab and ramucirumab (9.0% and 8.3%, respectively). Although several studies suggested that ramucirumab dose not increase the hazard of TE, the results are not consistent among studies.[32–34] In a Phase 2 study comparing the efficacy of ramucirumab vs placebo in combination with platinum and pemetrexed in advanced NSCLC, the incidence rates of arterial and venous TE were 10.4% and 11.9%, respectively, which was similar to our results.[35] Prospective studies are required to compare the efficacy as well as safety between these two antiangiogenic agents.

The major limitation of this study was its retrospective nature. Although the data were collected retrospectively, we tried to ensure the validity of patients' characteristics, treatment course, genetic alterations, as well as the outcome evaluation. We included a relatively large patient cohort and tried to make meaningful descriptions of the incidence, risk factors, and influence on outcomes of TE among advanced NSCLC patients receiving antiangiogenic therapy.

In conclusion, TE occurred in 10.1% of patients receiving antiangiogenic therapy. DVT was the most common TE and up to 46.2% of DVT did not occur in the typical lower extremities. With prompt diagnosis and treatment, the outcome of TE is usually favorable. As compared with patients without TE, TE with PD patients experienced a significantly shorter overall survival, but TE without PD patients had comparable survival time. The use of hormone analogue and proteinuria predicted the events among TE with PD group and TE without PD group, respectively. Owing to the different influences on the survival time and risk factors, TE with PD and TE without PD may be two different disease entities.

Data Sharing Statement

The data is not publicly available to protect patient privacy. Further details and other data supporting our study's findings are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB No. CF12019 and CF20175). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent for clinical data records and genetic testing was obtained from all patients.

Consent for Publication

All authors agreed to publish the paper in any form.

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Disclosure

The authors declare no conflicts of interest in this work.

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