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Incidence of venous thromboembolism in advanced lung cancer and efficacy and safety of direct oral anticoagulants: a multicenter, prospective, observational study (Rising-VTE/NEJ037 study)

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Abstract

Background: Venous thromboembolism (VTE) is a well-known type of cancer-associated thrombosis and a common complication of malignancy. However, the incidence of VTE associated with lung cancer and the effectiveness of direct oral anticoagulants remain unclear. This study aimed to identify the incidence of VTE associated with lung cancer at the time of diagnosis or during treatment, the efficacy and safety of edoxaban, and associated risk factors.

Methods: The Rising-VTE/NEJ037 study was a multicenter prospective observational study. Altogether, 1021 patients with lung cancer who were unsuitable for radical resection or radiation were enrolled and followed up for 2 years. Patients with VTE at the time of lung cancer diagnosis started treatment with edoxaban. The primary endpoint of this trial was the rate of newly diagnosed VTE after enrollment or recurrence rate 6 months after treatment initiation.

Results: Data were available for 1008 patients. The median age was 70 years (range: 30–94 years), and 70.8% were men. Sixty-two patients had VTE at the time of lung cancer diagnosis, and 38 (9.9%) developed VTE at follow-up. No cases of VTE recurrence were recorded 6 months after treatment initiation with edoxaban. Major and clinically relevant non-major bleeding events occurred in 4.9% of patients and increased to 22.7% in the edoxaban treatment group.

Conclusions: VTE occurrence should be monitored during lung cancer treatment. Although treatment with edoxaban was highly effective in preventing VTE recurrence, its administration should be cautiously considered because of the high bleeding rate.

Trial registration: jRCTs061180025.

Keywords: anticoagulants, cancer, lung neoplasms, pulmonary embolism, venous thromboembolism, venous thrombosis

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Introduction

Venous thromboembolism (VTE) during cancer treatment is a common medical complication, and the risk of VTE development is 4–20 times greater in patients with cancer than in those without cancer.[1,2] The number of cancer-associated

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VTE cases has been increasing yearly,[3] and its prognosis is poor.[4] In particular, lung cancer carries a high risk of VTE,[2] chemotherapy increases the risk of VTE,[5,6] and the increased use of drugs in lung cancer treatment contributes to a high risk of inducing VTE (e.g. angiogenesis inhibitors). As advancements in cancer chemotherapy now allow patients with lung cancer to hope for long-term survival,[7] managing complications, such as VTE, has become increasingly important.

Contrast-enhanced computed tomography (CT) and lower-extremity venous ultrasound are standard diagnostic approaches for VTE[8]; however, large-scale prospective studies with an intensive screening at the time of diagnosing the disease stage of lung cancer and the complication rate of VTE are scarce. The American Society of Clinical Oncology has categorized risk factors for cancer-associated VTE into cancer-related factors (cancer type and stage), treatment-related factors (surgery and use of chemotherapy), patient-related factors [age, body mass index, performance status (PS), smoking, and concomitant medical comorbidities], and biomarkers.[1] Nonetheless, many details of risk factors for VTE developing during the clinical course of lung cancer remain unclear, including whether the presence or absence of a driver gene mutation is a risk factor.[9] Therefore, there are no clear screening guidelines for identifying the risk of VTE in patients with lung cancer.

Given the multiple reports[10,11] indicating the usefulness of direct oral anticoagulants (DOACs), the current standard of care for cancer-associated VTE is DOAC or low-molecular-weight heparin (LMWH) administration.[1,8] Edoxaban (EDO), a DOAC, has been shown to be non-inferior to LMWH in the Hokusai-VTE Cancer trial, a randomized phase III trial involving patients with cancer-associated VTE, including lung cancer, in which the primary endpoint was VTE recurrence or major bleeding events (12.8 *versus* 13.5%, $p = 0.006$).[10] Therefore, EDO is widely used in the treatment of cancer-associated VTE; nevertheless, considering the high prevalence of major bleeding events depending on the type of cancer, patients who should receive EDO must be carefully screened.

Hence, the Rising-VTE/NEJ037 study, a multicenter prospective observational study on patients with lung cancer, was conducted. We aimed to identify the incidence of VTE associated with lung cancer at the time of diagnosis or during treatment, the efficacy and safety of EDO, and the associated risk factors.

Materials and methods

Patients

The main eligibility criteria were diagnosis of small cell lung cancer or non-small cell lung cancer based on cytological or histological examinations; the impossibility of conducting radical surgery, radiotherapy, and chemotherapy (regardless of disease stage); postoperative recurrence or disease recurrence after radical radiotherapy, or the conditions for which the best supportive care is suitable; an Eastern Cooperative Oncology Group PS of 0–3; patients aged ⩾20 years at the time of consent; and expected survival time of >6 months after consent.

As this was an observational study, there were no exclusion criteria for case enrollment. For EDO administration, the main exclusion criteria were patients who had a history of hypersensitivity to EDO; reduced kidney function (creatinine clearance <30 mL/min); an alanine aminotransferase level that was ⩾2-fold of the site standard or a total bilirubin level ⩾1.5-fold of the site standard; a liver disease accompanied with blood clotting abnormality; history or complications of radiation pneumonitis or interstitial lung disease; active bleeding or a high risk of bleeding; and patients taking aspirin ⩾100 mg/day or ⩾2 antiplatelet drugs. Among the patients identified with VTE complications at screening, those who met the main exclusion criteria were designated the observation group while those who did not satisfy these exclusion criteria were classified as the EDO group. All patients provided written informed consent.

Study design and treatment

This was a multicenter prospective observational study. Patients who met the eligibility criteria were checked for the presence or absence of VTE by contrast-enhanced chest-to-lower-extremity CT scan or contrast-enhanced chest-to-pelvic CT scan plus lower-extremity venous ultrasound. They were classified into either the observation group without VTE or the cancer-associated VTE group. The diagnosis of VTE was confirmed via a central review conducted by two radiologists. Additionally, patients in the cancer-associated

VTE group who did not meet the exclusion criteria and could receive EDO treatment were categorized into the EDO group, whereas those who violated the exclusion criteria and, thus, could not receive EDO treatment were categorized into the cancer-associated VTE observation group. These three groups, namely, the observation, EDO, and cancer-associated VTE observation group, were monitored for 2 years. Moreover, in the EDO group, the presence or absence of VTE recurrence was assessed 6 months after treatment initiation using the same testing modality as that used at the time of enrollment. The diagnosis and recurrence of VTE were confirmed via a central review performed by two radiologists. The incidence rate of bleeding events over 2 years after enrollment was examined in all groups.

The primary endpoints were the incidence rate of VTE over 2 years after enrollment and the VTE recurrence rate over 6 months after the EDO treatment initiation in the EDO group. The secondary endpoints were the incidence rate of bleeding events, the incidence rate of arterial thrombosis, and overall survival. We also investigated the patient background to identify risk factors for VTE co-development in patients with lung cancer.

Deep vein thrombosis

Patients with proximal deep vein thrombosis (DVT; popliteal vein, femoral vein, or iliac vein thrombosis) identified by contrast-enhanced CT or lower-extremity venous ultrasound were diagnosed with DVT that required treatment. Patients with isolated distal DVT (thrombosis found only in the soleus vein, sural vein, posterior tibial vein, or anterior tibial vein) who were asymptomatic were re-tested 2 weeks later using the same testing modality as that used at the time of diagnosis; patients with enlargement or progression of proximal thrombosis were diagnosed with DVT that required treatment.

Pulmonary thromboembolism

If thrombotic embolism occurred, the lobe artery or main pulmonary artery was scanned by using contrast-enhanced CT.

Arterial thrombosis

All acute arterial embolisms, newly developed strokes, and myocardial infarctions were considered arterial thrombosis.

Bleeding events

Bleeding events were assessed according to the International Society on Thrombosis and Hemostasis criteria.[12] Clinically evident bleeding that met at least one of the following conditions was considered major bleeding: decrease in hemoglobin level by $\geqslant$2 g/dL, transfusion of $\geqslant$2 units (500 mL/unit) of packed red blood cells or whole blood; bleeding in critical areas (intracranial bleeding, intraspinal bleeding, intraocular bleeding, pericardial bleeding, intra-articular bleeding, intramuscular bleeding accompanied by compartment syndrome, and retroperitoneal bleeding); and fatal bleeding. Meanwhile, bleeding that did not meet the criteria for major bleeding but was deemed clinically important according to the discretion of the attending physician was considered clinically relevant non-major bleeding.

Statistical analyses

The target sample size of the Rising-VTE/NEJ037 study was aimed to exceed the large-scale cohort reported so far because the VTE complication rate in Japanese patients with lung cancer was unknown at the time of planning the study. As the prospective cohort trial at that time included hundreds of cases, the target sample size of this trial was set to 1000 cases.

The primary endpoints of this study were the recurrence rate of symptomatic/asymptomatic VTE over 6 months of EDO treatment in the EDO group and the incidence rate of symptomatic/asymptomatic VTE over 2 years after enrollment in the observation group. These were calculated by dividing the number of symptomatic and asymptomatic VTE cases (or the number of recurrent cases) by the number of enrolled cases.

As a secondary endpoint, the incidence rate of bleeding events was calculated by dividing the number of cases with confirmed bleeding events by the number of cases enrolled in this study. Additionally, the incidence rate of symptomatic/asymptomatic VTE (recurrence rate and incidence rate of bleeding events) and overall survival over 2 years after enrollment in the observation, EDO, and cancer-associated VTE observation groups were compared using Fisher's exact test. Extraction of VTE risk factors was performed by multivariate logistic regression analysis as an exploratory analysis. All statistical analyses were performed using SPSS Statistics version 24.0 (IBM Japan, Ltd., Tokyo, Japan).

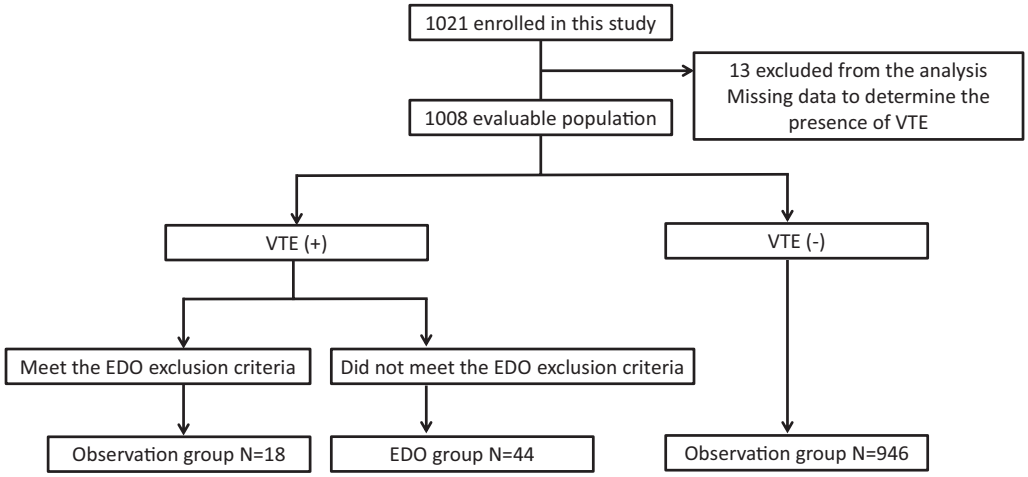


Figure 1. Cluster classification for VTE screening.
VTE, venous thromboembolism.

Results

Patient characteristics

This multicenter, prospective, observational study involved 35 participating Japanese institutions (Supplemental Table 1). It included 1021 patients diagnosed with lung cancer who were unsuitable for radical resection or radiation between June 2016 and August 2018. Among these, 13 patients had missing diagnostic imaging data necessary for enrollment, and the remaining 1008 were analyzed as the full analysis set (Figure 1).

The median age of the enrolled patients was 70 years (range: 30–94 years), and most patients were men (714 patients, 70.8%). Many patients had a good PS (0–1), accounting for 80.6% of the full analysis set. The most common histological subtype of lung cancer was adenocarcinoma in 641 (63.6%) patients, followed by small-cell lung cancer in 137 (13.6%) patients. The disease stage was assessed according to the seventh edition of the Union for International Cancer Control TNM (tumor, node, metastasis) staging system for lung cancer,[13] and M1a and M1b stage IV diseases accounted for 80% of the cases (Table 1).

Primary outcomes

Herein, 62 patients had VTE at the time of lung cancer diagnosis, and 38 patients developed VTE after a 2-year follow-up. The incidence rate of VTE in the observation group ($n=946$) over 2 years after enrollment, which was the primary endpoint, was 4.0% (38 patients). No VTE recurrence was observed in the EDO group ($n=44$) over 6 months after the EDO treatment initiation nor was there any case of VTE recurrence when the patients were observed for 2 years (Table 2(a)).

Secondary outcomes

The incidence rate of arterial thromboembolism (ATE) over 2 years after enrollment, which was the secondary endpoint, was 3.4% (32 patients). Moreover, the incidence rates of ATE were high at 15.9% in the EDO group with confirmed VTE co-development at the time of lung cancer diagnosis and at 11.1% in the cancer-associated VTE observation group (Table 2(b)). Major and clinically relevant non-major bleeding occurred in 4.9% of the observation group, whereas it increased to 22.7% in the EDO group at 6 months. Even in terms of bleeding events identified by follow-up during the 2-year period, the incidence rate of bleeding events was 10.0% in the observation group, in which the patients had not have co-developed VTE at the time of lung cancer diagnosis, whereas the incidence rate in the EDO group increased to 34.1% (Figure 2). By contrast, major bleeding accounted for 26.5 and 25% of the bleeding events in the observation and EDO groups, respectively. No treatment-related deaths due to bleeding were observed in the registered patients. The most common cause of major bleeding in the observation group was the transfusion of >2 units (500 mL/unit) of packed red blood cells, and bleeding from an important area was observed in the cancer-associated VTE group (Supplemental

Table 1. Patient characteristics at the time of lung cancer diagnosis.

All *N* = 1008	All *N* = 1008	With VTE *N* = 62	Without VTE *N* = 946	*p*-Value
Age (years)				
Median	70	70	71	0.841
Range	30–94	41–81	30–94	
Sex (%)				
Male	714 (70.8)	33 (53.2)	681 (72.0)	0.005
Female	294 (29.2)	29 (46.8)	265 (28.0)	
ECOG PS (%)				
0	403 (40.0)	15 (24.2)	388 (41.0)	0.001
1	490 (40.6)	35 (56.5)	455 (48.1)	
2	74 (7.3)	4 (6.5)	70 (7.4)	
3	41 (4.1)	8 (12.9)	33 (3.5)	
Histological type (%)				
Adenocarcinoma	641 (63.6)	55 (88.7)	586 (61.9)	0.017
Squamous	187 (18.6)	4 (6.5)	183 (19.3)	
Small cell	137 (13.6)	1 (1.6)	136 (14.4)	
Others	43 (4.3)	2 (3.2)	41 (4.3)	
Clinical stage (%)				
T factor				
T1	160 (16.8)	9 (16.1)	151 (16.9)	0.431
T2	255 (26.8)	22 (39.3)	233 (26.0)	
T3	213 (22.4)	8 (14.3)	205 (22.9)	
T4	287 (30.1)	15 (28.8)	272 (30.4)	
Tx	37 (3.9)	2(3.6)	35 (3.9)	
Missing	56	6	50	
N factor				
N0	195 (20.2)	8 (13.8)	187 (20.7)	0.196
N1	98 (10.2)	6 (10.3)	92 (10.2)	
N2	268 (27.8)	10 (17.2)	258 (28.5)	
N3	402 (41.7)	34 (58.6)	368 (40.7)	
Missing	45	4	41	

(Continued)

Table 1. (Continued)

All *N* = 1008	All *N* = 1008	With VTE *N* = 62	Without VTE *N* = 946	*p*-Value
M factor				
M0	192 (20.0)	5 (8.6)	187 (20.7)	0.024
M1a	228 (23.8)	9 (15.5)	219 (24.3)	
M1b	540 (56.3)	44 (75.9)	496 (55.0)	
Missing	48	4	44	

The *p*-value was calculated using the Kruskal–Wallis or chi-squared method. Clinical stages were assigned according to the seventh edition of the Union for International Cancer Control TNM staging system for lung cancer.[13]
ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Summary of the study's results.

(a) Recurrence or newly diagnosed VTE.

	VTE (−) follow-up group (%) *N* = 946	VTE (+) EDO treatment group (%) *N* = 44	VTE (+) follow-up group (%) *N* = 18
Recurrence (or newly diagnosed) VTE for 6 months	19 (2.0)	0	–
Recurrence (or newly diagnosed) VTE for 2 years	38 (4.0)[a]	0	–

EDO, edoxaban; VTE, venous thromboembolism.
[a]Primary endpoint.

(b) Newly diagnosed ATE.

	VTE (−) follow-up group (%) *N* = 946	VTE (+) EDO treatment group (%) *N* = 44	VTE (+) follow-up group (%) *N* = 18
Newly diagnosed ATE for 2 years	32 (3.4)	7 (15.9)	2 (11.1)

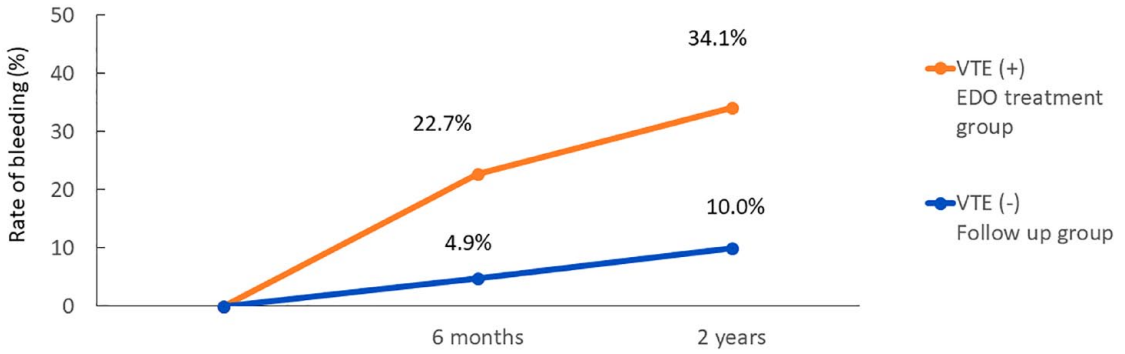
ATE, arterial thromboembolism; EDO, edoxaban; VTE, venous thromboembolism.

Figure 1a). No major differences were observed between the two groups in terms of the breakdown of clinically relevant non-major bleeding, and approximately half of the bleeding events occurred in the respiratory tract in both groups (Supplemental Figure 1b). The median survival was 24.0 months (95% confidence interval [CI]: 16.8–not estimable) in the EDO group and 19.2 months (95% CI: 16.8–21.6) in the observation group, indicating no significant difference ($p = 0.793$) (Supplemental Figure 2).

Among the 100 patients with co-developed VTE, 55% of them had DVT, and 22% of them had both pulmonary thromboembolism (PE) and DVT (Figure 3(a)). Moreover, only 25% of the VTE cases were symptomatic, and asymptomatic cases were very common regardless of when they were diagnosed (coinciding with a lung cancer diagnosis or during 2 years of follow-up monitoring) (Figure 3(b)).

Identification of risk factors for VTE

In the multivariate analysis of patient background (age, sex, PS, medical history, comorbidities, and concomitant medications), tumor factors (histological subtype and TNM factors), and



Severity of bleedings	Events	Major bleeding	Non-major bleeding
VTE (+) EDO treatment group (%), N=44	20	5 (25)	15 (75)
VTE (-) follow up group (%), N=946	113	30 (26.5)	83 (73.5)

Figure 2. The rate and severity of bleedings.
VTE, venous thromboembolism; EDO, edoxaban.

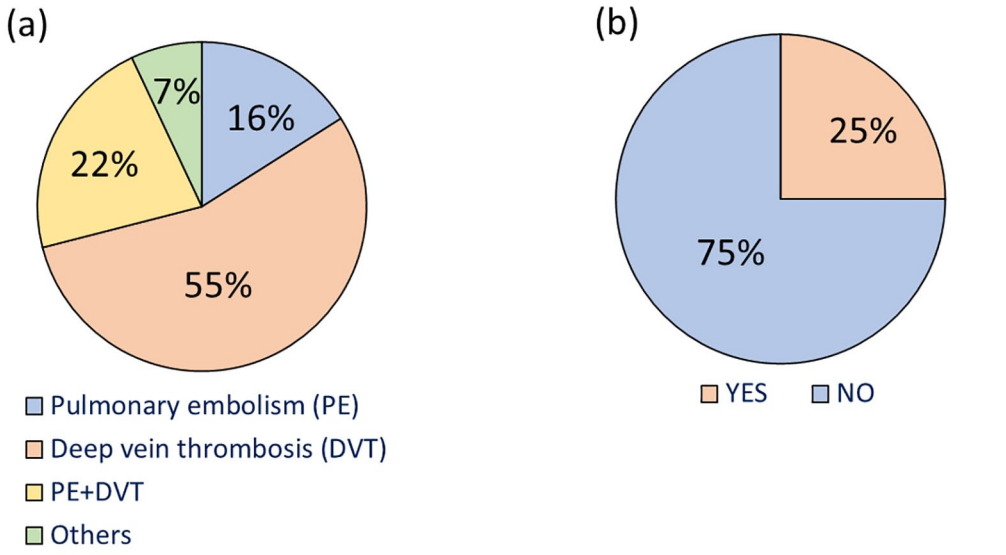


Figure 3. The rate of VTE type (a) and symptoms at diagnosis (b).
VTE, venous thromboembolism.

results from physiological and blood biochemistry tests (complete blood cell count, liver and kidney function indicators, electrolytes, oxygen saturation, and blood pressure), the female sex, adenocarcinoma, N3, poor PS, low lymphocyte count, low platelet count, high prothrombin fragment (PT F) 1+2, and high diastolic blood pressure (DBP) were identified as risk factors for VTE (Table 3).

Herein, 91.2% of the patients enrolled received chemotherapy with tyrosine kinase inhibitors, immune checkpoint inhibitors, and cytotoxic anticancer agents after enrollment. Thus, whether

Table 3. Risk factors for VTE were identified using logistic regression analysis.

Parameters	OR	95% CI	*p*-Value
Sex			
Female	2.18	1.31–3.63	0.003
Histology			
Adenocarcinoma (*versus* non-small cell, others)	2.23	1.22–4.10	0.009
N type			
N1 (*versus* N0)	1.83	0.63–5.34	0.269
N2 (*versus* N0)	1.36	0.57–3.27	0.486
N3 (*versus* N0)	2.78	1.29–6.01	0.009
ECOG PS			
1 (*versus* 0)	2.12	1.18–3.79	0.012
2 (*versus* 0)	1.63	0.61–4.39	0.333
3 (*versus* 0)	2.29	0.74–7.09	0.149
LYMPH			
Per 1%	0.96	0.93–0.99	0.017
Patient count			
Per $5 \times 10^4/\mu L$ fluctuation	0.97	0.95–1.00	0.031
PT F1+2			
Per 50 pmol/L fluctuation	1.08	1.03–1.14	0.003
DBP			
Per 1	1.02	1.00–1.04	0.054

CI, confidence interval; DBP, diastolic blood pressure; ECOG PS, Eastern Cooperative Oncology Group performance status; LYMPH, lymphocyte; OR, odds ratio; PT F, prothrombin fragment.

the administration of chemotherapy would be a risk factor for VTE was not investigated.

Discussion

To the best of our knowledge, the Rising-VTE/NEJ037 study is the largest prospective study where intensive screening of VTE was conducted at the time of lung diagnosis, and further follow-up was conducted to examine the incidence of VTE.

Herein, the VTE co-development rate over 2 years was 9.9%, which was approximately the same or slightly lower than that reported in studies conducted in Western countries[14,15] that examined the incidence rate of VTE in patients with lung cancer (7.8–13.9%) and studies conducted on Japanese patients (10.8%).[16] For cases of asymptomatic isolated distal DVT, this study adopted the criteria that confirmed DVT diagnosis during retesting 2 weeks later using the same testing modality as that at the time of diagnosis, indicating enlargement or progression of proximal thrombosis. Thus, only patients with DVT for whom the guidelines clearly recommend treatment[1] have been enrolled in the study as cancer-associated VTE cases. A previous report[17] has suggested that the incidence rate of VTE is low among Asians, and thus, the incidence rate of VTE that at least requires treatment in Asian patients during the

management of lung cancer is approximately the same as that reported in Western patients. Moreover, even if we similarly analyze only DVT requiring treatment, 75% of VTE cases were asymptomatic, and cancer-associated VTE may be actively diagnosed by screening.

The DOAC or LMWH administration is recommended as the standard treatment for cancer-associated thrombosis.[1,8] EDO, a type of DOAC, is an oral drug taken once daily that directly inhibits the factor Xa in the coagulation cascade and exerts an anticoagulant effect. The Hokusai-VTE cancer trial, a randomized phase III trial that investigated the efficacy and safety of LMWH *versus* EDO, the standard treatment for cancer-associated thrombosis, has demonstrated that LMWH was non-inferior to EDO in terms of the incidence rate of VTE recurrence and major bleeding, the combined endpoint of the study, which was 12.8% in the EDO group and 13.5% in the LMWH group (HR: 0.97, 95% CI: 0.70–1.36, $p = 0.006$).[10] Here, the patients with confirmed VTE co-development at the time of lung cancer diagnosis were treated with EDO, and the efficacy of EDO in routine clinical practice was prospectively investigated. In the EDO group, no VTE recurrence was recorded at 6 months or after monitoring for 2 years, which was the primary endpoint of the study, showing the efficacy of EDO for cancer-associated VTE. However, evaluating the risk of bleeding as an adverse event of EDO is crucial. In the subset analysis of major bleeding events in the Hokusai-VTE cancer trial, the incidence rate of bleeding events was higher in the EDO group than in the LMWH group (6.9 *versus* 4.0%). During the 6-month and 2-year follow-up periods of this study, the incidence rate of bleeding events was higher in the EDO group than in the observation group. Nevertheless, no significant differences were noted between both groups in terms of the number of fatal bleeding or proportion of all bleeding events and major bleeding accounted for. No cases of death or treatment discontinuation due to bleeding in the EDO group were recorded. As a result of a meta-analysis of four clinical trials that compared the efficacy and safety of DOACs for cancer-associated VTE with those of LMWH,[18] DOACs demonstrated significant results in terms of their ability to suppress VTE recurrence. However, DOACs are associated with a significantly increased incidence of bleeding events, particularly clinically relevant non-major bleeding compared with LMWH; managing bleeding is important when using DOACs. Great care should be taken when administering anticoagulant therapy to patients with residual tumor-exposed lesions on the mucosal surface, as well as patients with an apparent bleeding tendency.

The analysis of the survival period did not reveal a distinct difference between the EDO and observation groups. Hence, aggressive screening for VTE associated with lung cancer was performed in patients at a high risk of co-development or development, and therapeutic intervention with DOAC for patients with cancer-associated VTE is recommended after considering the risks and benefits. Therefore, identifying patients who require aggressive screening at the time of lung cancer diagnosis is important, so we analyzed the background of patients with cancer-associated VTE. We identified the female sex, adenocarcinoma, N3, poor PS, low lymphocyte count, low platelet count, high PT F1+2, and high DBP as risk factors for VTE co-development.

Moreover, two placebo-controlled trials have demonstrated the usefulness of LMWH for preventing VTE in patients with cancer scheduled for chemotherapy.[19,20] Recently, two placebo-controlled trials investigating the preventive effect of DOACs on VTE in patients with cancer scheduled for chemotherapy with a Khorana *et al.*[21,22] score of $\geqslant 2$ have demonstrated the efficacy of preventive oral administration of DOACs. However, despite that this study was conducted before the publication of efficacy data of DOACs, a meta-analysis of randomized controlled trials on VTE prevention by pharmacotherapy, which included data from > 5000 patients, has indicated that preventive treatments did not affect overall survival.[23] Moreover, preventive administration did not increase the frequency of bleeding,[19] although completely reducing the risk of bleeding is desirable. Hence, developing a risk scoring system to accurately ascertain patients who would benefit from preventive treatments is important. Based on this study's findings, we plan to create a pre-chemotherapy risk prediction score for the development of VTE associated with lung cancer.

This study had some limitations. First, chemotherapy did not examine the increased risk of VTE, as >90% of the patients enrolled in the study received chemotherapy. Additionally, the effect of VTE initiation on the discontinuation or delay of chemotherapy has not been investigated. Second, as contrast-enhanced chest CT was performed to evaluate metastatic status, rather than

dynamic CT to evaluate PE, the cumulative incidence of PE may be lower in this study. Third, because this study was conducted in Japan and insurance coverage for the use of LMWH for cancer-associated thrombosis has not been approved, a study determining whether DOACs or LMWH is safer for use in routine clinical practice can be difficult to conduct.

Nevertheless, the data from this large-scale prospective study that conducted intensive screening during cancer diagnosis are important for the implementation of effective and safe cancer treatments for patients with lung cancer.

Conclusions

Aggressive screening demonstrated that the incidence rate of VTE in Asian patients was not different from that in Western patients. While EDO, a DOAC for lung cancer-associated VTE, was very highly effective, it is necessary to carefully determine the indication for DOACs by thoroughly assessing each individual patient for the risk of bleeding. Being female and having adenocarcinoma are well-known risk factors for VTE that co-develop with lung cancer, and our study has also newly suggested PT F1+2 as a risk factor.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Shimane University Institutional Review Board (approval date; November 30, 2015, No. 2015) based on the Clinical Trials Act enacted in Japan in 2017. This study was published in the Japan Registry of Clinical Trials list (jRCTs061180025, registration date; February 20, 2019). All patients provided written informed consent.

Consent for publication

All authors have read the manuscript and approve its submission to Therapeutic Advances in Medical Oncology.

Author contributions

Yukari Tsubata: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Takamasa Hotta: Data curation; Investigation; Methodology; Writing – review & editing.

Kosuke Hamai: Investigation; Writing – review & editing.

Naoki Furuya: Investigation; Writing – review & editing.

Toshihide Yokoyama: Investigation; Writing – review & editing.

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Competing Interests

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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