



Venous thromboembolism in patients with severe lung cancer: a narrative review

Lin-Xin Zheng^{1#}, Li Li^{1#}, Jin-Hai Huang¹, Yu-Mei Mai¹, Can Chen¹, Jia-Hui Dong^{2,3}, Zhi-Yong Xu⁴, Wei-Feng Li¹, Xiao-Rong Chen⁵

¹Department of Pulmonary and Critical Care Medicine, General Hospital of Southern Theater Command, Guangzhou, China; ²Department of Medical Intensive Care Unit, General Hospital of Southern Theater Command, Guangzhou, China; ³Guangzhou Key Laboratory of Geriatric Infection and Organ Function Support, Guangzhou, China; ⁴Department of Radiation Oncology, General Hospital of Southern Theater Command, Guangzhou, China; ⁵Clifford Hospital, Guangzhou, China

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[#]These authors contributed equally to this work.

Correspondence to: Prof. Wei-Feng Li. Department of Pulmonary and Critical Care Medicine, General Hospital of Southern Theater Command, Guangzhou 510010, China. Email: lwf980622@126.com.

Objective: At present, there are several guidelines for cancer complicated with VTE, but there is no specific recommendation for the treatment of lung cancer complicated with VTE. Whether is necessary to explore treatment and prevention of VTE in lung cancer.

Background: Venous thromboembolism (VTE) is a common complication of severe lung cancer that can entail many adverse effects for patients. The incidence of VTE is higher in patients with lung cancer than in those with other kinds of solid tumors, and it is especially high among patients with lung adenocarcinoma, at advanced tumor-node-metastasis (TNM) stages, or with a history of central venous catheter (CVC) or chemotherapy. However, the clinical symptoms of VTE in patients with lung cancer are not typical and cannot be detected easily, and the clinical prevention rate is low. In the acute phase of VTE in lung cancer, the Eastern Cooperative Oncology Group (ECOG) performance status score of patients typically ranges from 2 to 4 points, leaving end-stage maintenance therapy as the only treatment option.

Methods: Here, we analyze the existing literature and discuss the current status (including epidemiology, clinical manifestations, and risk factors), risk assessment tools, and the treatment and prevention of VTE in severe lung cancer. We focus particularly on the use of low-molecular-weight heparin and new oral anticoagulants (including in the management of thrombocytopenia after antitumor therapy) in lung cancer patients with VTE.

Conclusions: Large-scale prospective multicenter studies on the treatment and prevention of VTE in lung cancer are necessary.

Keywords: Lung cancer; venous thromboembolism (VTE); phylaxis; risk assessment

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Introduction

Advanced severe lung cancer refers to patients with stages IIIB, IIIC, and IV lung cancer whose Eastern Cooperative

Oncology Group (ECOG) performance status score is in the range of 2 to 4 due to causes related to the lung cancer itself or complications of anti-tumor drugs, at the same time these patients have a high probability of benefiting

from the existing systemic anti-tumor treatments (1). Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most frequent cardiovascular event after stroke and MI (myocardial infarction) in Western countries (2). Many studies have shown that the prevalence of VTE is significantly increased among patients with lung cancer compared to patients with other cancers. VTE can appear before cancer diagnosis, and before the start of lung cancer treatment, patients may be in a hypercoagulable state (3). Some investigations have shown that patients with lung cancer have the highest incidence of thrombotic events among all cancer patients (4). The related mechanisms of malignant tumor progression include direct invasion and external compression of blood vessels, injury of endothelial cells caused by chemotherapeutics, factor X activation and tissue factor expression from tumor cells, blood platelet activation and aggregation, and expression of inflammation factors caused by tumor, such as von Willebrand factor VIII (5). The occurrence of VTE often increases the severity of lung cancer patients' conditions, leading to a poor prognosis. One study reported that among 94 cases of non-small cell lung cancer (NSCLC) after pneumonectomy, thrombosis was found in lung tumor tissue and nearby non-cancerous tissue in 56 cases (59.6%); there were 24 cases (25.5%) of pulmonary artery thrombosis and 32 cases (34.0%) of pulmonary vein thrombosis. After 2 years of follow-up, the results showed that patients with thrombosis had a lower survival rate compared to patients without thrombosis (6). We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/apm-21-1281>).

Status

Epidemiology

In 2018, GLOBOCAN data showed that lung tumor is the most common cause of cancer mortality in many places around the world (7). Between all cancer patients and the general population, the hazard-ratio of VTE is 4.7 (8). Thrombosis is the leading cause of death among all cancer patients (9). Lung tumor patients are more likely to develop VTE than other cancer patients, with an incidence of 13.9% (10). Compared to that of the general population, the VTE risk ratio is elevated 20-fold for patients with lung cancer. In particular, patients with lung adenocarcinoma have a higher risk of VTE than those with lung squamous cell carcinoma. Furthermore, for patients undergoing

radiotherapy or chemotherapy, and for those with metastatic disease, the risk is also heightened (11). One study found that the incidence of VTE was remarkably higher among cancer patients than among non-cancer patients (12), especially in lung cancer patients during anticoagulant therapy, the occurrence rate of VTE could reach 27% (13). Patients with prolonged ICU length of stay, femoral central venous catheter, or a high Caprini score may have an increased risk of developing VTE, despite the use of guideline-recommended thromboprophylaxis, the cumulative incidence of VTE at 28 days of ICU stay was up to 9.55% (14). The proportion of COVID-19 patients with VTE was 6% in ward patients (15).

Clinical manifestations

Lung cancer patients with PE may present with symptoms including dyspnea, chest pain, hemoptysis, and syncope (16). In a study of 113 lung cancer patients, 88.5% of patients with VTE were symptomatic, and the rest were asymptomatic (17).

Risk factors

Lung cancer-related risk factors for VTE

Pathological types and stages

In a meta-analysis of 16 studies, the results showed that advanced tumor stage (TNM III–IV *vs.* I–II) and a history of adenocarcinoma were the clinical features of lung cancer patients with PE compared to those without PE (16). Another Cox regression analysis indicated that independent risk factors for VTE included metastatic disease and the adenocarcinoma subtype (18). The risk of VTE is higher for patients with adenocarcinoma than for patients with squamous cell carcinoma, especially for those with metastasis (11).

Gene mutation

A multicenter, retrospective cohort study investigated the incidence of VTE in patients with C-ros oncogene 1-receptor tyrosine kinase-positive (ROS1+), anaplastic lymphoma kinase-positive (ALK+), Kirsten rat sarcoma viral oncogene-positive (KRAS+), and epidermal growth factor receptor-positive (EGFR+) lung cancer. The study found that in comparison with patients with KRAS+ and EGFR+ lung cancer, patients with ROS1+ lung cancer had a significantly increased risk of VTE. The thromboembolic incidence among patients in the ALK+ NSCLC group was also found to be lower than that in the ROS1+ group, although multivariable analysis showed there to be no significant differences between the two groups (19).

The METROS (Analysis From a Phase II, Prospective, Multicenter, Two-arms Trial) study showed that the incidence of VTE among patients with ROS1-rearranged NSCLC is 3 to 5 times higher than that in the general NSCLC population (20).

One study identified all patients with ALK-rearranged NSCLC diagnosed in Canada, and a confirmation cohort involving all eligible patients with ALK-rearranged NSCLC treated in Israel was enrolled. The overall VTE rate was 36%, and the incidence of VTE in this ALK-rearranged study population was 3 to 5 times larger than that in the general NSCLC population (21).

One retrospective case-control study included a total of 57 cases with VTE and 102 cases without VTE from 2000 to 2009. The odds ratio of thrombosis in patients with EGFR+ NSCLC was 0.99, compared with 2.67 in the KRAS+ group, thus showing a higher incidence of VTE in the latter group (22).

All of the abovementioned studies indicate that patients with ROS1+, ALK+, and KRAS+ NSCLC have an increased risk of VTE (19-22), while EGFR+ mutation may have no effect to the occurrence of VTE in NSCLC patients (22).

Treatment-related risk factors

Chemotherapy

VTE is a common disease in patients with lung tumors, especially among those receiving chemotherapeutic regimens. In most cases, VTE occurs within 6 months after the start of chemotherapeutic treatment, and the occurrence of VTE has been found to be closely associated with an increased risk of mortality in these patients (23).

Another retrospective study was performed of patients with lung cancer who underwent platinum-based chemotherapy from a national inpatient database in Japan. Using multivariable logistic regression analysis, the authors reported that compared with a carboplatin (CBDCA)-based or nedaplatin (CDGP)-based regimen, cisplatin-based chemotherapy carried a stronger risk of VTE (24). These two studies showed that chemotherapeutics increase the incidence of VTE for lung tumor patients, with cisplatin-based chemotherapy carrying a higher risk of VTE than other chemotherapeutic regimens.

Antiangiogenesis

Among advanced NSCLC patients, the use of anti-vascular endothelial growth factor (VEGF) drugs can significantly increase the risk of arterial thromboembolic events (ATEs), but not VTEs. Clinicians should be aware of the risk of severe ATEs with the use of these drugs (25). Several studies have shown that bevacizumab alone or in combination with

chemotherapy increases the risk of VTE in cancer patients; however, the relationship between bevacizumab and VTE risk in lung cancer patients has rarely been reported (26,27).

Patient-related risk factors

Age

Lower age is associated with a higher VTE risk among lung cancer patients. For patients under the age of 45 years old, the incidence of VTE is about 3 times higher than that among patients aged over 75 years old (28).

Ethnicity

Race is also a risk factor for VTE in lung cancer patients. In the general population, the incidence of VTE varies among races, with African Americans and Asians having the highest and the lowest incidence, respectively (29).

Complications

Patients with atrial fibrillation and chronic kidney disease are more likely to suffer VTE (30). Incidence of recurrent VTE was seemingly not related to the development of chronic thromboembolic pulmonary hypertension in patients after a first episode of pulmonary embolism (31,32).

Prognosis

The Nationwide Inpatient Sample (NIS) was analyzed by one study and involved all lung tumor in patients from 2006 to 2010 in the United States. Among these inpatients, those with VTE had a higher death rate, higher medical costs, greater disability, and a longer length of stay than those without VTE (33). Acute symptomatic VTE deeply affects the living quality of patients with malignant tumors (34). Both PE and major bleeding are associated with an increased risk of death and could be indicators of lung cancer mortality (35).

Treatment of VTE in patients with severe lung cancer

At present, there are no specific guidelines for the treatment of lung cancer with VTE. However, lung cancer is regarded as an important factor in many prediction models for cancer with VTE. Therefore, the treatment of lung cancer with VTE may have its own characteristics. Here, we refer to the authoritative guidelines on cancer with VTE and discuss the treatment of lung tumor with VTE.

Low-molecular-weight heparin

Before 2002, vitamin K antagonists (VKAs) were the main anticoagulant therapy for tumor complicated with

VTE. However, patients with lung cancer undergoing chemotherapy or targeted therapy often experience vomiting or diarrhea, which affects the absorption of VKAs, making the international normalized ratio (INR) value difficult to control. Moreover, there were interactions among VKAs and commonly used chemotherapeutic or targeted drugs for lung cancer, such as gemcitabine, paclitaxel, etoposide, carboplatin, and tyrosine kinase inhibitors. The 2002 Canthanox trial opened a new era of low-molecular-weight heparin (LMWH) in the treatment of cancer complicated with VTE. LMWH has many advantages, such as having a short half-life and less interaction with chemotherapeutic or targeted drugs, and being less affected by food. Subsequently, many clinical studies have been conducted to evaluate the effectiveness and safety of LMWH.

The CANTHANOX study was a stochastic, multicentric trial involving 146 tumor patients with VTE. The trial compared warfarin with subdermal enoxaparin (1.5 mg/kg once a day) over a period of 3 months. The results showed that warfarin is associated with a higher rate of bleeding in tumor patients with VTE, and prolonged treatment with enoxaparin sodium may be more effective and safer for these patients. This trial established the position of LMWH in the treatment of tumor complicated VTE (36).

In their meta-analysis of 1,169 cancer patients in 3 RCTs, Martínez-Zapata *et al.* aimed to evaluate the safety and efficacy of Tinzaparin in the treatment of VTE in cancer patients compared with other anticoagulants. The results of the meta-analysis suggested that short- and long-term treatment with Tinzaparin was superior to VKA treatment in preventing VTE recurrence (37).

Data from the CLOT study were analyzed for comparison of the efficacy and safety of dalteparin and VKAs for recurrent venous thromboembolism (rVTE) prevention in patients with cancer and kidney injury. The results confirmed that the incidence of rVTE could be decreased considerably by dalteparin compared with VKAs, and with better safety (38).

Direct oral anticoagulants

The Hokusai-VTE Cancer Clinical Trial was a non-inferiority, open-label study of 1,046 patients to compare the composite outcomes of patients with recurrent VTE or primary bleeding treated with edoxaban or dalteparin. Patients were split into two groups: the first group was given 60 mg of edoxaban every day after receiving LMWH for

at least 5 days, and the second group was given 200 IU/kg subdermal dalteparin every day for 1 month followed by 150 IU/kg subdermal dalteparin every day. The treatment was given for at least 6 months and for up to 12 months in both groups. The trial results confirmed that oral edoxaban was non-inferior to dalteparin in the recurrent composite outcome of VTE of main bleeding (39).

A randomized, multicenter, open-label pilot study, the SELECT-D trial, aimed to evaluate rivaroxaban as a selective therapy for VTE in cancer patients. In total, 203 sick people were randomly divided into two groups to receive dalteparin (150 IU/kg every day for 1–5 months after 1 month of 200 IU/kg daily) or rivaroxaban (20 mg once daily for 6 months after 15 mg twice a day for 3 weeks). The trial showed that rivaroxaban was associated with a lower rate of VTE than dalteparin; however, the incidence of primary bleeding and clinical relative secondary bleeding in the rivaroxaban group was increased (40).

Two multicenter, randomized trials (41,42) were conducted to compare the risk of VTE recurrence and main bleeding between apixaban and dalteparin. The ADAM VTE trial was a superiority trial that included 287 patients, and the Caravaggio clinical trial was a non-inferiority trial involving 1,155 patients. Patients in both trials were given subdermal dalteparin (150 IU/kg daily after 200 IU/kg of body weight daily for the first month) or oral apixaban (5 mg twice a day after 10 mg twice a day for 7 days) for at least half a year. The results of the two trials showed that compared with subdermal dalteparin, oral apixaban could reduce the recurrence rate of cancer-related VTE, without increasing the risk of massive hemorrhage.

Management of thrombocytopenia after antitumor therapy

The International Society on Thrombosis (ISTH) (43) and the British Committee for Standards in Haematology (BCSH) (44) recommend a full-dose anticoagulant therapy for patients with cancer-related VTE who have a platelet count over $50 \times 10^9/L$. For patients whose platelet count is between 25×10^9 and $50 \times 10^9/L$, the ISTH recommends full-dose anticoagulant therapy plus platelet transfusion until the platelet count reaches the empirical threshold, while the BCSH recommends half-dose anticoagulant therapy. However, the American Society of Clinical Oncology (ASCO) (45), BCSH, and ISTH all state that anticoagulation is contraindicated for severe thrombocytopenia patients [those with a platelet count below $25 \times 10^9/L$ (BCSH and ISTH) or $20 \times 10^9/L$ (ASCO)].

Inferior vena cava filter

In a prospective randomized trial, patients with PE and/or DVT were randomly divided into two groups. All patients received anticoagulant therapy with fondaparinux sodium; one group received a vena cava filter placement, while the other group did not. Neither group showed advantages in terms of safety, recurrence, or survival (46). As an international prospective, multicenter, single-arm clinical trial, the Crux Inferior Vena Cava Filter System study involved 125 patients implanted with the Crux filter. Follow-up lasted for 180 days after filter placement and for 30 days after filter retrieval, the data showed that treatment was successful in 96.0% of patients, with high rates of technical, clinical, and retrieval success, the Crux vena cava filter performed well (47). Patients with acute PE and DVT who have absolute contraindications for anticoagulants have an extremely poor clinical prognosis, but there is no high-quality prospective studies to support the use of an inferior vena cava (IVC) filter (44). One study analyzed the CENTRAL, MEDLINE, LILACS, and EMBASE databases, and used the Cochrane Collaboration's instrument and a modified version for cohort research to assess the risk of bias. A fixed-effects analysis of 7 studies involving 35,333 patients was conducted. The majority of research items indicated a low risk of bias. Among cancer patients, vena cava filter implantation has no benefits for preventing recurrent VTE (48). The absence of random clinical experiments, as well as conflicting results from retrospective studies, preclude evidence-based judgment on the efficacy and safety of IVC filters for patients who have an absolute contraindication to anticoagulants. Moreover, emerging data on IVC filter-related complications emphasize that IVC filters should be used with caution (49). To conclude, the benefits of IVC filters in the treatment of VTE are not clear, and more high-quality studies still need to be conducted.

Prevention of VTE in patients with advanced severe lung cancer

Risk assessment tool

Khorana risk score

The Khorana score can be used to predict the risk of VTE for symptomatic cancer patients in hospital and is an assistive model for tailoring anticoagulant thromboprophylaxis in such hospitalized patients (50). One study used this simple model to assess the risk of VTE

in tumor patients beginning chemotherapy and found it to be a reliable model based on 5 clinical and laboratory parameters. It could identify patients with an almost 7% short-term risk of VTE, and may be used to tailor anticoagulant thromboprophylaxis in outpatients (51).

Vienna score (expanded risk model of the Khorana score)

A study used the Vienna score, which is an expanded risk model based on the Khorana score, and found a statistically significant difference in the cumulative incidence of VTE between patients with the highest risk score and those with an intermediate risk score. The hazard ratio of the patients with the highest grade to those with the lowest grade was 25.9. Five clinical and standard laboratory parameters of the Khorana score with the addition of biomarkers (soluble P-selectin, and D-Dimer) can predict VTE and identify cancer patients who are at high or low risk of VTE (52).

Protecht score

The Protecht model adds 1 point for therapy with carboplatin or cisplatin-based chemotherapy or gemcitabine, and 2 points for association with the score based on the 5 predictive variables of the Khorana score. Compared to the Khorana score, this score model has been reported to have an improved capacity to distinguish patients who are at high risk of VTE (53).

The ONKOTEV study

The ONKOTEV study, which was based on Khorana score >2, took various clinical parameters into account, including a history of previous VTE, the compression of vascular/lymphatic structures by the tumor, and the presence of metastatic disease. It offered a promising model to improve primary prophylaxis for cancer outpatients (54).

COMPASS-CAT

Compared with the Khorana score, the COMPASS-CAT risk assessment model contains easily collected and reliable VTE risk parameters. The variables included in this risk assessment model are shown in *Table 1*. The COMPASS-CAT model is more suitable for patients with common solid tumors after the initiation of anticancer therapy (55).

One retrospective external validation study of cancer patients undergoing active therapy indicated that, while the discrimination of the COMPASS-CAT risk assessment model for VTE was moderate and the model calibration was poor, the model had a good negative predictive value (56).

Table 1 Predictive simplified VTE score for antitumor therapy in general cancer inpatients

Predictors for VTE	Score ^a
Cancer-related risk factors	
Anti-hormonal therapy for women with hormone receptor-positive breast cancer or on anthracycline treatment	6
Time since cancer diagnosis 6 months	4
CVC	3
Advanced stage of cancer	2
Predisposing risk factors	
Cardiovascular risk factors (composed by at least two of the following predictors: personal history of peripheral artery disease, ischemic stroke, coronary artery disease, hypertension, hyperlipidemia, diabetes, obesity)	5
Recent hospitalization for acute medical illness	5
Personal history of VTE	1
Biomarkers	
Platelets count $\geq 350 \times 10^9/L$	2

^a, low/intermediate risk: 0–6; high risk: 7. CVC, central venous catheter; VTE, venous thromboembolism.

TiC-Onco risk score

The TiC-Onco risk assessment tool takes into account two new parameters, patient genetics and clinical information, in its examination of risk factors for VTE. One study showed that this model can perform better in identifying cancer patients who have a high risk of VTE compared to the Khorana score (57).

Two variables

Data from the prospective Vienna Cancer and Thrombosis Study cohort was used to select predictive variables for a clinical prediction model. Finally, two variables (tumor-site risk category and continuous D-dimer concentration) were chosen for the predictive tool. Compared to previous predictive tools for cancer-related VTE, this simple model represents an important improvement, and it also makes it easier for doctors to identify patients who could benefit from thromboprophylaxis (58).

Performance of risk assessment tools in lung cancer

In both multivariable and univariate analyses, the patients were predominantly older males with NSCLC, a high-risk Khorana score (a score of >2) was not associated with risk of VTE compared to an intermediate score (a score of 1–2), as high-risk Khorana risk score could not distinguish patients who were at the highest risk of VTE, but a high-risk Khorana score was a predictor of lung cancer mortality (59). CANTARISK is a prospective, global, non-interventional cohort study, clinical data were selected before the end of the 6-month follow-up. Univariable and multivariable Cox regression analyses showed that the Khorana score was an important predictor of early mortality, but it was not suitable for predicting the risk of VTE inpatients with lung malignancies in the era of targeted therapy (60). One study assessed several models: the PROTECHT score, COMPASS-CAT, CONKO score, and Khorana risk score. Only the COMPASS-CAT score had the ability to distinguish VTE accurately and was characterized by good differentiation among high- and low-risk patients with VTE. Comparing all VTE risk assessment models, this study indicated that COMPASS-CAT had the best performance in precisely predicting VTE in lung cancer patients (30).

The prevention of VTE in patients with severe lung cancer

At present, there is no specific guideline for the prevention of VTE in lung cancer patients. Here, we refer to the major guidelines for the treatment of cancer complicated with VTE and the relevant literature on lung cancer with VTE, and discuss the drug-based prevention of VTE in hospitalized and outpatient lung cancer patients undergoing chemotherapy.

Hospitalized patients

Critically ill patients are at an increased risk of VTE due to unique risk factors: prolonged immobilization, invasive lines and devices, certain medications, and acquired thrombophilia. Furthermore, VTE in the critically ill is associated with increased duration of mechanical ventilation, increased length of intensive care unit and hospital stay, and a trend toward increased mortality.

Clinical practice guidelines therefore recommend VTE prophylaxis with either subcutaneous heparin or low-molecular-weight heparin for all critically ill patients without contraindication (61). However, no trials have assessed inpatient thromboprophylaxis in patients with lung malignancies. Three randomized controlled trials (RCTs) involving cancer inpatients showed that compared with the placebo, thromboprophylaxis could reduce the incidence of VTE without increasing the risk of massive hemorrhage. However, a meta-analysis of these three RCTs, which covered VTE incidents as a main outcome and analyzed it on the basis of cancer patient subgroups, found that the risk ratio of VTE events in hospitalized cancer patients undergoing thromboprophylaxis was 0.91, and thromboprophylaxis was found to lack efficacy in these patients (62).

Ambulatory patients with cancer undergoing systemic chemotherapy

The PROTECHT and TOPIC-2 studies were two randomized, double-blind, placebo-controlled studies which evaluated the clinical benefits of VTE prophylaxis in advanced cancer patients undergoing chemotherapy. A combined subgroup analysis of the two studies included 811 lung cancer patients (532 patients in the TOPIC-2 study and 279 patients in the PROTECHT study). All patients accepted active prophylaxis: certoparin 3,000 IU once daily subcutaneously for 6 months (TOPIC-2 study) or nadroparin 3,800 IU once daily subcutaneously for up to 4 months (PROTECHT study) (63). According to these studies, preventive treatment with LMWH could reduce the risk of VTE in cancer patients, including those with locally advanced lung cancer who were undergoing chemotherapy (59).

The SAVE-ONCO study was a double-blind, multicenter trial comparing the safety and efficacy of subcutaneous semuloparin (20 mg once daily) to that of a placebo in cancer patients receiving chemotherapy. A total of 1,608 patients received semuloparin, and 1,604 received the placebo. The results showed that semuloparin lowered the risk of VTE occurrence in malignant tumor patients undergoing chemotherapy, without obviously raising the risk of major bleeding (64).

AVERT was a double-blind, controlled, randomized clinical trial that evaluated the safety and efficacy of apixaban (at a dose of 2.5 mg twice a day) for thromboprophylaxis in outpatients with malignant tumors who were undergoing chemotherapy and had a Khorana score of ≥ 2 . Altogether,

563 patients were included in the modified intention-to-treat analysis. The results showed that apixaban can significantly reduce the risk of VTE; however, it can also increase the incidence of main bleeding (61).

CASSINI was a double-blind, randomized trial which compared the safety and effectiveness of rivaroxaban (10 mg once daily) with that of a placebo for up to 180 days in high-risk ambulatory cancer patients with a Khorana score ≥ 2 . A total of 1,080 patients were enrolled. Rivaroxaban resulted in an observably reduced risk of VTE and did not increase the risk of major bleeding (65).

Central venous catheters (CVCs)

A meta-analysis of 13 RCTs assessed the harms and benefits of LMWH, VKAs, unfractionated heparin (UFH), or fondaparinux, and evaluated the outcomes produced by medicines among cancer patients with CVCs. The results showed that the effect of LMWH and VKA on patients with catheters was not conclusive; however, moderate-certainty evidence that LMWH reduced catheter-related VTE compared to no LMWH was found. Therefore, we should balance the possible benefit and harms when considering anticoagulation in patients with cancer with CVCs (66). Another study randomly assessed intervention with warfarin (at a low dose) for cancer patients carrying CVCs and showed that warfarin (at a dose of 1 mg daily) did not decrease the risk of VTE for these patients (67). Another study found that treatment with primary thromboprophylaxis in cancer patients carrying CVCs was neither beneficial nor harmful (68). The Good Clinical Practices Guidelines (GCPG) suggest that anticoagulant treatment for routine prophylaxis is not recommended for CVC-related thrombosis (CRT), and the best places for CVC placement are the right jugular vein and the junction of the right atrium and the superior vena cava (69).

Conclusions

Lung cancer combined with VTE has adverse effects on patients, but its diagnosis can easily be missed due to the symptoms and signs of lung cancer itself. Many risk factors can lead to VTE in lung cancer patients, including advanced disease and adenocarcinoma, chemotherapy and antiangiogenic therapy, and KRAS+, ROS+, or ALK+ NSCLC. In terms of chemotherapy, cisplatin-based regimens carry a higher incidence of VTE than carboplatin/nedaplatin-based regimens. VEGF drugs can

also significantly increase the risk of advanced arterial thromboembolic (ATE). Finally, among lung cancer patients, younger age, certain races (e.g., African Americans), and comorbidities are also high-risk factors for VTE. At present, there are no specific guidelines for the treatment and prevention of VTE in lung cancer, and large-scale, prospective, multicenter studies are also lacking in this area. Therefore, herein, we referred to the recommendations of the relevant guidelines for cancer with VTE and the related research on lung cancer with VTE, and discussed the prevention and treatment of VTE in lung cancer.

Compared with warfarin, enoxaparin can reduce thrombosis-related mortality. Long-term use of enoxaparin may be safer for cancer patients. Dalteparin sodium significantly reduces the risk of rVTE in patients with cancer and kidney damage, and shows comparable safety. In terms of the prevention of VTE recurrence, tinzaparin is superior to VKAs as a short- and long-term treatment. Compared with dalteparin sodium, edoxaban had a lower rate of VTE recurrence but a higher incidence of massive hemorrhage. With rivaroxaban, the recurrence rate of VTE was reported to be lower than that with dalteparin, while the incidence of clinically relevant non-main bleeding was increased. Apixaban shows better efficacy in the treatment of malignant tumor-associated VTE and does not increase the risk of massive hemorrhage. These 3 new oral anticoagulants can be used as alternatives to LMWH in patients with tumor with VTE. In addition, the guidelines point out that when the platelet count exceeds $50 \times 10^9/L$, there is no effect on the anticoagulation of LMWH. However, when the platelet count reaches $(25-50) \times 10^9/L$, anticoagulation therapy should be the half-value dose and be stopped when the platelet count is $\leq 25 \times 10^9/L$. Furthermore, there is no high-quality evidence that IVC filters are beneficial in the treatment of acute VTE. The Khorana score is the main prediction model used to select cancer outpatients for thromboprophylaxis. This model has been improved many times. It is suitable for use as a predictive tool for thromboprophylaxis in lung cancer outpatients; however, the COMPASS-CAT model may be more suitable for thromboprophylaxis in these patients.

In terms of VTE prevention, no trial has assessed thromboprophylaxis in hospitalized lung cancer patients. Patients receiving chemotherapy regimens (gemcitabine and cisplatin or carboplatin) may benefit more from the use of nadroparin in the prevention of thrombosis. Ultra-LMWH sodium semuloparin is also effective and safe for preventing VTE in cancer patients undergoing

outpatient chemotherapy. For high-risk outpatients receiving chemotherapy (Khorana score ≥ 2), apixaban can significantly reduce the risk of VTE at the start of chemotherapy, although it carries a high incidence of massive hemorrhage. Rivaroxaban significantly reduces the incidence of such events during the intervention period. In addition, anticoagulant therapy is not recommended for routine prevention of CRT in cancer patients with CVCs.

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