

## ORIGINAL ARTICLE

# Efficacy and safety of chemotherapy for newly diagnosed advanced non-small cell lung cancer with venous thromboembolism

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## Keywords

Chemotherapy; non-small cell lung cancer; venous thromboembolism.

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## Abstract

**Background:** Venous thromboembolism (VTE) is a serious complication in patients with lung cancer. The benefit of chemotherapy for lung cancer patients with VTE remains unknown. This study was conducted to elucidate the efficacy and safety of chemotherapy for advanced non-small cell lung cancer (NSCLC) in patients with VTE.

**Methods:** Newly diagnosed patients with advanced (i.e. stage IIIB and IV) NSCLC with VTE who received systemic chemotherapy were studied. Response rates, progression-free survival (PFS), overall survival (OS), and toxicity were retrospectively analyzed.

**Results:** In this study, 21 patients who received chemotherapy plus anticoagulation therapy between December 2009 and February 2011 were included. The objective response and disease control rates within the first regimen were 14.29% (3/21) and 76.19% (16/21), respectively. The median PFS, one-year survival rate, and median OS were 5.50 months, 33.30%, and 8.70 months, respectively. The main grade 3/4 toxicities observed included neutropenia (28.57%), nausea 4 (19.05%), and anemia 2 (9.52%). Major bleeding was not observed.

**Conclusion:** Chemotherapy for newly diagnosed patients with advanced NSCLC and VTE was feasible and had acceptable toxicity; however, the survival of these patients remained inferior to that of patients without VTE.

## Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication and the leading cause of death in lung cancer patients.<sup>1–4</sup> The incidence of VTE is 7.3–13.6% in lung cancer patients.<sup>1–3,5,6</sup>

In patients with both early and advanced stage non-small cell lung cancer (NSCLC), VTE occurs more frequently in patients who receive chemotherapy.<sup>3,7–10</sup> One study reported that the incidence of VTE after chemotherapy was 10.8 per 100 person-years and the median time to occurrence was 109 days.<sup>7</sup> Another study revealed that three to 12 months after chemotherapy, the incidence of VTE was 13.9%.<sup>10</sup> The presence of a VTE event is significantly associated with an

increased risk of mortality.<sup>1,7</sup> VTE is a significant predictor of death within two years in both NSCLC and small cell lung cancer (SCLC).<sup>1</sup> Patients with VTE have a substantially lower survival rate than patients without VTE, as predicted from a competing risk analysis of survival (13% vs. 60% at 18 months).<sup>11</sup> Moreover, lung cancer patients who receive chemotherapy and develop VTE have significantly shorter survival.<sup>7</sup> To date, there have been few studies evaluating the incidence, timing, and risk factors of VTE associated with chemotherapy in lung cancer patients.<sup>1,12</sup> There are no specific reports evaluating the clinical efficacy of chemotherapy for lung cancer with VTE. The purpose of this study was to investigate the efficacy of chemotherapy for newly diagnosed advanced NSCLC patients with VTE. In addition, we examined the adverse events that occurred during treatment.

## Materials and methods

### Study population

From December 2009 to February 2011, hospitalized patients with newly diagnosed NSCLC who met the following criteria were included in the study: (i) histologically or cytologically confirmed advanced (stage IIIB or IV) NSCLC; (ii) accompanying VTE; (iii) chemotherapy as the only anti-cancer therapy; and (iv) Eastern Cooperative Oncology Group (ECOG) performance status (PS) was within the range of 0–2. All clinical and laboratory data were collected retrospectively.

Venous thromboembolism was diagnosed by venous ultrasound, computed tomography (CT) venography, CT pulmonary angiography, magnetic resonance imaging pulmonary angiography, or pulmonary ventilation/perfusion scan. With regard to the anticoagulation of VTE, we paid particular attention to bleeding events. The outcomes of VTE were defined as fatal pulmonary embolism (PE), dissolution, recurrence, post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension. The ethics committee of the Beijing Chao-Yang Hospital, Capital Medical University approved the study (No. 2009-4).

### Efficacy and adverse reactions

Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The observation indicators included complete remission (CR), partial response (PR), stable disease (SD), disease progression (PD), objective response rate (ORR), and disease control rate (DCR). Evaluation of treatment response by CT scan was repeated every four to eight weeks. Progression-free survival (PFS) was defined as the time from the first medication to the first objective progression of disease. Overall survival (OS) was measured as the period from diagnosis of lung cancer to death. Follow-ups of PFS and OS commenced from the end of treatment, every three months, until 25 August 2013. Deaths were identified by reviewing the hospital-chart records or telephone follow-up. The evaluation of adverse reactions was based on the National Cancer Institute Common Toxicity Criteria (CTC) Version 3.0.

### Statistical analysis

Continuous variables were summarized as medians with interquartile ranges (IQR) or means and standard deviation. For categorical variables, the percentages of patients in each category were calculated. The median OS and PFS were estimated using the Kaplan–Meier method. A *P* value of <0.05 was considered statistically significant. All analyses were

performed using SPSS software for Windows (Version 17.0, SPSS Inc., Chicago, IL, USA).

## Results

### Characteristics of patients

A total of 482 newly diagnosed lung cancer patients were enrolled in this study. Four hundred and twenty-one patients were excluded, as they did not develop VTE. Thirty-five patients were excluded because they received best support therapy, Chinese medicine, surgery, or epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs, such as gefitinib or erlotinib) as first-line therapy. Two patients were excluded because they could not tolerate chemotherapy because their PS was > 2. Three patients had SCLC and were, therefore, excluded. Finally, 21 eligible and consecutive patients were included in our study (Figure 1).

There were 14 men and seven women in this study, with an average age of  $58.21 \pm 13.5$  years. Tumor histology included 85.7% (18/21) adenocarcinomas, and 14.3% (3/21) squamous cell carcinomas. At the time of recruitment, one patient (4.8%) was in stage IIIB and 20 (95.2%) were in stage IV. Of the 21 included patients, 10 suffered DVT, four suffered PE, and seven suffered DVT and PE (Table 1). All patients received anticoagulant therapy for VTE. The baseline physiological data are shown in Table 2.

### First-line chemotherapy and its response

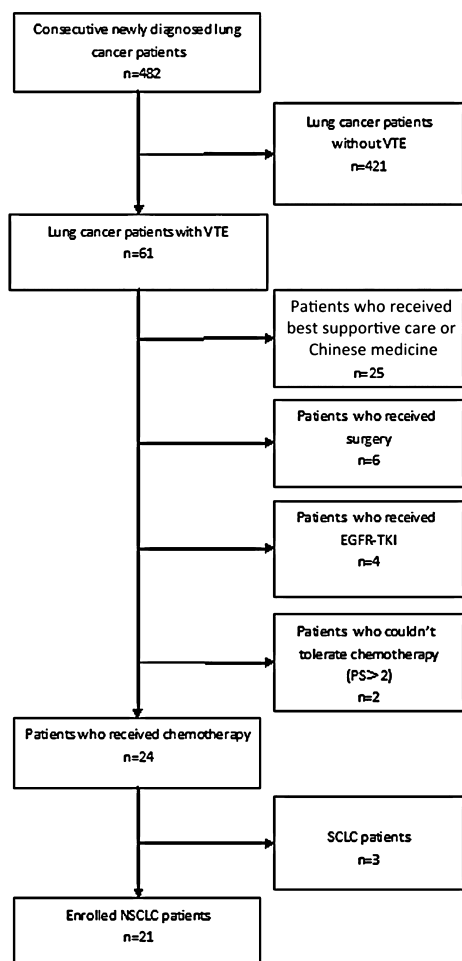
In Table 3, the ORR of the first regimen is shown. The most frequently selected regimen was platinum combined with gemcitabine (86.70%). The total ORR was 14.29%. SD was observed in 13 patients and PD was observed in five patients. Mean cycles of applied first-line chemotherapy were  $2.95 \pm 1.50$  (range: 1–5 cycles; 95% confidence interval [CI] 2.27–3.63). None of the patients received maintenance therapy and 10 patients received second-line or further treatment.

### Overall survival and progression-free survival of first-line chemotherapy

We performed a survival analysis on 25 August 2013; the data are shown in Figures 2 and 3. The median OS was 8.70 months (95% CI 6.62–10.78) and the one-year survival rate was 33.30% (Figure 2). The median PFS of the first regimen was 5.50 months (95% CI 3.61–7.29) (Figure 3).

### Management and outcome of venous thromboembolism

All included cases presented asymptomatic or nonspecific symptoms when VTE was found. Anticoagulation therapy



**Figure 1** Analysis profile. All 21 enrolled cases were advanced (stage IIIB or IV) non-small cell lung cancer (NSCLC) patients with venous thromboembolism (VTE). EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; SCLC, small cell lung cancer.

was performed after VTE diagnosis, and continued during chemotherapy. VTE in 12 patients was dissolved with subcutaneous injection of low molecular weight heparin (LMWH). Eight patients suffered chronic VTE; one patient experienced post-thrombotic syndrome presented as limb pain and lower limb swelling, even though they received anticoagulation. None of the patients developed fatal PE.

**Toxicity**

Of the 21 patients treated with chemotherapy and anticoagulation, three experienced bleeding: one acute upper gastrointestinal bleeding, one slight epistaxis for one week, and one patient presented with hemoptysis; however, major bleeding was not observed. Treatment-related adverse events other than bleeding are listed in Table 4. The most common hema-

**Table 1** Characteristics of all NSCLC patients

Male : Female	14:7
Age (years)	58.21 ± 13.51
ECOG	
0	1
1	16
2	4
Smoking (pack-years)	29.50 ± 17.49
Histology	
Adenocarcinoma	18
Squamous cell carcinoma	3
Stage	
NSCLC	
IIIB	1
IV	20
VTE	
DVT	10
PE	7
DVT + PE	4

Data are presented as mean ± standard deviation or number. DVT, deep venous thromboembolism; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PE, pulmonary embolism; SCLC, small cell lung cancer; VTE, venous thromboembolism.

tological grade 3/4 adverse events were neutropenia (28.57%), anemia (9.52%), and thrombocytopenia (4.76%). The only non-hematological grade 3/4 adverse event observed was nausea (9.52%).

**Table 2** NSCLC physiological data

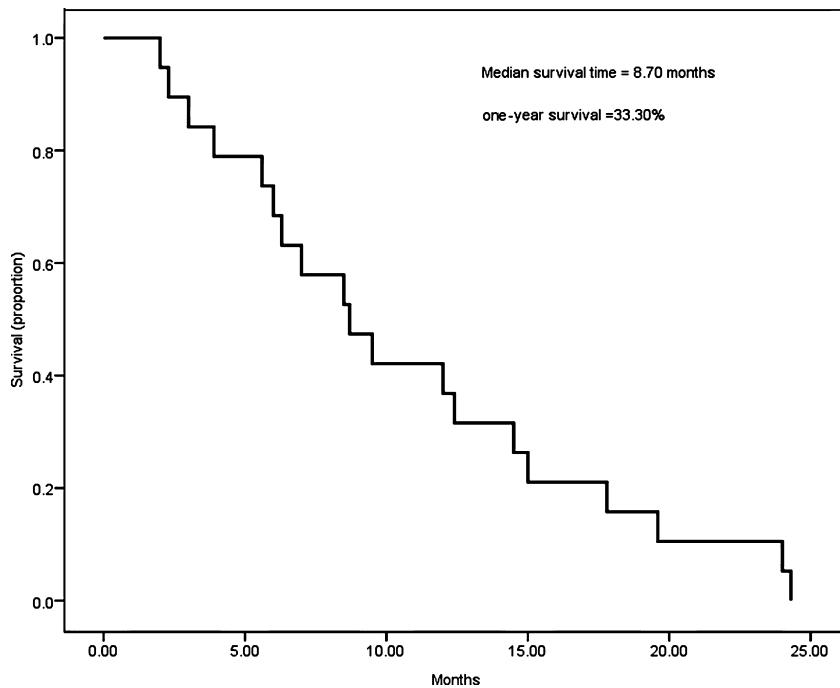
WBC (×10 <sup>9</sup> /L)	8.40 ± 3.67
HGB (g/L)	131.14 ± 22.29
PLT (×10 <sup>12</sup> /L)	238.57 ± 80.04
CRP (mg/dl)	2.39 (0.33–5.30)
CEA (ng/ml)	4.55 (0.43 to 35.91)
D-Dimer (ng/ml)	1590.00 (1024.27–2610.43)

Data are presented as mean ± standard deviation, median and inter quartile range. CEA, carcinoembryonic antigen; CRP, creative response protein; HGB, hemoglobin; NSCLC, non-small cell lung cancer; PLT, platelet; WBC, white blood cells.

**Table 3** NSCLC response to first-line chemotherapy

Regimen	n	ORR	DCR
Gemcitabine + carboplatin/cisplatin	15	20.0% (3/15)	86.7% (13/15)
Gemcitabine	2	0.0% (0/2)	0.0% (0/2)
Vinorelbine + cisplatin	2	0.0% (0/2)	100.0% (2/2)
Paclitaxel + carboplatin	1	0.0% (0/1)	0.0% (0/1)
Docetaxel + carboplatin	1	0.0% (0/1)	100.0% (1/1)
Total	21	14.29% (3/21)	76.19% (16/21)

DCR, disease control rate; n, number of patients; NSCLC, non-small cell lung cancer; ORR, objective response rate.

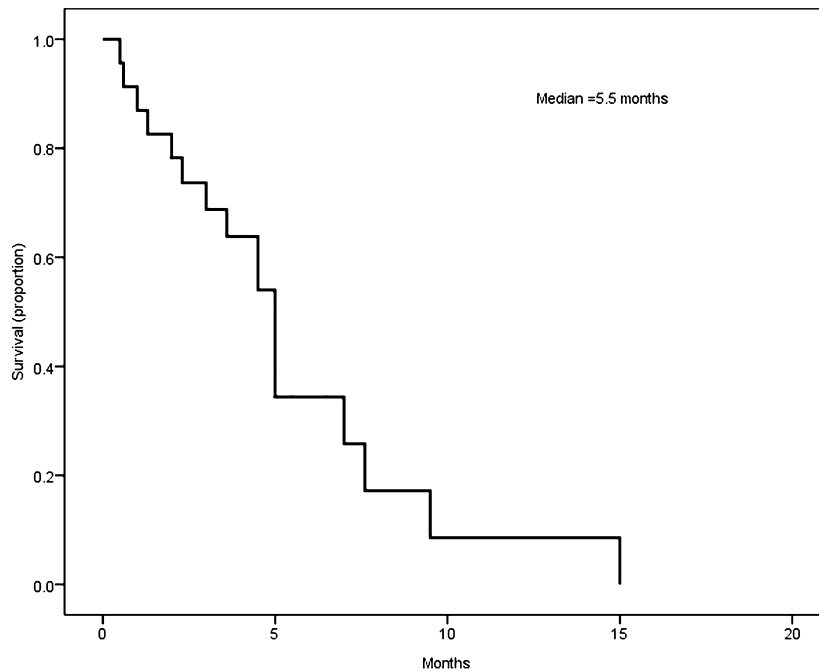


**Figure 2** Overall survival: the median and one-year survival was 8.70 months and 33.30%, respectively.

**Discussion**

To our knowledge, this is the first report that describes the benefit of chemotherapy specifically in NSCLC patients with

VTE. We evaluated the clinical efficacy of systemic chemotherapy for newly diagnosed patients with advanced NSCLC and VTE. The PR and SD of the first regimen, median PFS, median OS, and one-year survival rates were 14.29% (3/21),



**Figure 3** The median progression-free survival was 5.5 months.

**Table 4.** Adverse events

Toxicity	Grade 3/4(%)
Anemia	2 (9.52)
Neutropenia	6 (28.57)
Febrile neutropenia	3 (14.28)
Thrombocytopenia	1 (4.76)
Nausea	4 (19.05)

Data are presented as a number or proportion.

61.90 % (13/21), 5.50 months, 8.70 months, and 33.30%, respectively. These results suggest that chemotherapy for advanced NSCLC with VTE had comparable efficacy to chemotherapy for NSCLC without VTE.

In this study, the most frequently selected regimen was cisplatin plus gemcitabine. The response rate for cisplatin/gemcitabine (20.0%) was lower than that reported in ECOG 1594 (21.0%) and studies by Sandler *et al.* (30.4%) and Grigorescu *et al.* (29%).<sup>13–15</sup> In the three previous studies using this regimen, the median OS rates were 8.8, 9.1, and 11.5 months, and the one-year survival rates were 36%, 39%, and 36%, respectively; that is, comparatively good survival was demonstrated.<sup>13–15</sup> The ORR and PFS in this study were comparable to those observed in ECOG 1594. However, the OS in this study was unsatisfactory for patients with VTE. There are several possible reasons for this difference. First, only 10 of the 21 patients received second-line or further treatment because EGFR-TKI and pemetrexed were not widely available in China at that time of our study. Second, our patients might have had a decreased PS during chemotherapy because of the respiratory impairments and functional limitations VTE caused and because chemotherapy was often delayed. Finally, four patients experienced rapid lung cancer progression and ceased chemotherapy.

In regards to toxicity, hematological toxicities were the most common and were manageable, and no severe non-hematological toxicities, other than nausea, were observed. The rate of grade 3/4 neutropenia (28.57%) in our study was lower than in the cisplatin/gemcitabine arm of the ECOG 1594 (39%) and Sandler *et al.* studies (35%) and the carboplatin/gemcitabine arm of the Grigorescu *et al.* and Sederholm *et al.* studies.<sup>13–16</sup> The rate of grade 3/4 nausea (19.05%) in our study was also lower when compared to the ECOG 1594 and Sandler *et al.* studies.

A previous study suggested that the risk of bleeding in lung cancer patients appeared higher with LMWH or warfarin usage.<sup>17</sup> Moreover, a meta-analysis revealed that both a vitamin K antagonist and LMWH increased the risk of hemorrhage in lung cancer patients without an indication for anticoagulants; however, LMWH did not increase the incidence of major bleeding.<sup>18</sup> Among the 21 patients in our study, three patients experienced manageable bleeding during anticoagu-

lation. Therefore, increased physician awareness and careful surveillance of the bleeding risk in NSCLC patients with VTE during chemotherapy is warranted to manage risks.

An early report showed that the risk of mortality was lower, including that in cancer patients, when LMWH was used in initial VTE treatment.<sup>19</sup> A multicenter, randomized controlled trial revealed that the use of LMWH was associated with improved survival in patients with solid tumors without metastatic disease at the time of an acute VTE event.<sup>20</sup> Moreover, another recent meta-analysis revealed that anticoagulation showed a one (relative risk [RR] 1.18, 95% CI 1.06 to 1.32;  $P=0.004$ ) and two-year (RR 1.27, 95% CI 1.04 to 1.56;  $P=0.02$ ) survival benefit for lung cancer patients without an indication for anticoagulants.<sup>18</sup> However, in a multicenter, randomized, open-label study, the outcomes did not show any survival benefit for nadroparin in patients with advanced NSCLC (stage IIIB).<sup>21</sup> A median survival of 12.1 months was observed in the nadroparin recipients compared to 10.1 months in the NSCLC patient no-treatment arm (hazard ratio [HR], 0.90; 95% CI, 0.60 to 1.33,  $p=0.59$ ). In addition, a recent meta-analysis did not show a survival benefit for cancer patients receiving LMWH, although it did suggest a reduction in thrombotic events.<sup>22</sup>

Chew *et al.* found that the one and two-year survival rates of patients with VTE were lower than those of patients without VTE in both NSCLC and SCLC cohorts. Survival at one and two years after diagnosis in advanced stage patients was lower than that of patients with a limited stage.<sup>1</sup> VTE was a significant predictor of death within two years for both NSCLC and SCLC (HR = 2.3, 95% CI = 2.2–2.4, and HR = 1.5, 95% CI = 1.3–1.7, respectively). In addition, a recent study revealed that in lung cancer patients receiving chemotherapy, the median OS in patients with PE, DVT, and both PE and DVT was 56, 156, and 131 days, respectively, which was significantly lower than patients without VTE. The presence of a VTE event is significantly associated with an increased risk of mortality in lung cancer patients.<sup>7</sup> In the present study, the median OS of advanced lung cancer patients with VTE was 8.70 months, combined systemic chemotherapy and anticoagulation was tolerated, and the toxicities were acceptable.

There are several limitations to this study. First, it was a small retrospective study to confirm the efficacy of chemotherapy for newly diagnosed NSCLC patients with VTE. A large prospective study is required in the future. Second, there were limited chemotherapy drugs available in China at the time of this study, and only a few patients received second-line or further treatment. Further studies are therefore needed to ascertain whether our results also apply to new agents. Third, it is possible that there was a greater tendency for NSCLC patients with VTE to be treated with best supportive care rather than systemic chemotherapy, compared to NSCLC patients without VTE.

## Conclusion

In conclusion, this study showed that chemotherapy for advanced NSCLC patients with VTE was feasible and had acceptable toxicities; however, survival in these patients remained inferior to that of patients without VTE. Future large prospective studies are required to address this issue.

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## Disclosure

No authors report any conflict of interest.

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