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Retrospective evaluation of thromboembolic events in patients with non-small cell lung cancer treated with platinum-based chemotherapy

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ABSTRACT

Objectives: Thromboembolic events (TE) are common in patients with cancer and are potentially life-threatening. In lung cancer, little is known about thrombosis during chemotherapy treatment. The aim of this study was to describe the incidence of TE in patients with non-small cell lung cancer (NSCLC), occurring during treatment with platinum-based chemotherapy.
Methods: We retrospectively selected patients with NSCLC treated with platinum-based chemotherapy at the VU University Medical Center Amsterdam between 2000 and 2012. Patients who underwent recent surgery were excluded. All TE were included that occurred from start of chemotherapy treatment until 30 days after last administration.
Results: Among 784 included patients, 63 (8.0%) patients had 69 TE during treatment. Forty-five venous TE (VTE) and 24 arterial TE (ATE). Six patients had multiple events within treatment period, 3 of which had simultaneous ATE and VTE. In total, 613 patients were treated with cisplatin, 119 patients received carboplatin and 52 patients received both in first- or second-line treatment. In 8% (55/665) of the patients exposed to cisplatin a TE had occurred vs. 5% (8/171) in patients exposed to carboplatin ($p = 0.42$). The majority of TE occurred in the first 2 cycles (70%). History of TE was related to occurrence of TE during chemotherapy ($p < 0.01$). Median PFS was similar in patients with and without TE (6.2 vs. 7.2 months, respectively; $p = 0.10$). Median OS was significantly shorter in patients with TE (9.5 vs. 12.9 months, respectively; $p = 0.03$).
Conclusion: In our series, both ATE and VTE were a common finding during chemotherapy. TE was a poor prognostic factor. No difference in TE incidence was found between patients treated with cisplatin or carboplatin.

1. Introduction

Thromboembolic events (TE) in cancer patients are a well described phenomenon since Trousseau established a relationship between cancer and thrombosis in 1865 [1]. Both venous and arterial thromboembolic events (VTE and ATE) in patients may be a first sign of cancer becoming symptomatic in the near future [2–5]. Between TE and cancer there is a two-way relationship. In cancer patients who develop VTE at time of diagnosis, a worse prognosis and a more advanced stage has been reported, suggesting that TE is a marker of more aggressive disease [6]. On the other hand, patients with known malignancy, have an increased risk on developing TE [7,8]. An overall 7-fold increased risk of VTE was reported in patients with malignancy compared to those without. In lung cancer patients a 22-fold risk increase was observed in one study [9]. Reported incidences of TE in cancer patients are as high as 20% [10]. This has a major influence on the patients' prognosis and increase morbidity rates, especially patients experiencing a pulmonary embolism or myocardial infarction [11].

It has been reported that cisplatin-based chemotherapy increases the risk of VTE [12]. The pathophysiology of cisplatin-related TE is poorly understood [13]. In lung cancer, platinum-based chemotherapy is standard as first-line treatment. Unfortunately, previous studies focussed on treatment with cisplatin only, thereby leaving the occurrence of TE in patients treated with carboplatin unaddressed. Carboplatin is believed to be the safer choice, with less renal toxicity and nausea/vomiting, but the incidence of TE during treatment with carboplatin is unknown [14]. The aim of our

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study is to evaluate the incidence of VTE and ATE during platinum-based chemotherapy in NSCLC patients.

2. Methods

2.1. Subjects

We retrospectively selected all patients with cytological or histological proven NSCLC who received platinum-based chemotherapy in the VU University Medical Center Amsterdam between January 2000 and October 2012. Patients were selected by searching hospital records of the Department of Pulmonary Diseases. Patients who had surgery (with general anesthesia) in the period of 6 months prior to platinum treatment till 30 days after the last chemotherapy administration were excluded. The following data were collected: age, sex, history of smoking, body mass index (BMI), recent surgery, history of previous TE, history of atrial fibrillation, history of myocardial infarction (MI), ECOG performance score (PS), histology, stage of disease, TNM classification, comorbidity, type of chemotherapy treatment, number of platinum chemotherapy cycles, date of start chemotherapy treatment, date of disease progression, date of last contact, date of death, date of TE, localization TE, treatment of TE.

2.2. Methods

Cisplatin or carboplatin was combined with one or two other agents. The choice of treatment was based on institutional policy unless patients were entered in a clinical trial. A TE was defined as an arterial or venous thrombosis or embolism of the larger blood vessels that occurred from the first day of chemotherapy treatment till 30 days after the last administration of treatment [15]. TE were diagnosed by Doppler echography, computer tomography angiogram or lung ventilation-perfusion scan. Myocardial infarction was diagnosed by physical examination, electrocardiography and laboratory findings.

Progression free survival (PFS) was defined as the time from start of treatment until objective tumor progression according to RECIST criteria, or death. Overall survival (OS) was defined as the time from start treatment until death or last date of contact.

2.3. Statistics

Primary objective was to describe the incidence of ATE and VTE in NSCLC patients during platinum treatment. Secondary objectives were to study differences in prevalence of TE between cisplatin- and carboplatin-based chemotherapy, and differences in PFS and OS in patients who developed TE during chemotherapy.

For categorical data, Chi-squared test was performed to test a possible relation with TE. The *t*-test was used for continuous variables and for comparing means. Survival analysis was performed by using Kaplan–Meier plot curves. Log-rank test was used to estimate differences in survival between subgroups. To estimate the hazard ratio (HR), Cox regression analysis was used. In a multivariate analysis, the following prognostic factors were included: age, PS and stage of disease.

3. Results

3.1. Baseline characteristics

A total of 839 patients were selected, of which 55 patients (7%) underwent surgery prior or short after chemotherapy treatment and subsequently excluded. In total, 784 patients were included in the analysis. Patient characteristics are described in Table 1. The mean age was 59 years (range 24–89), 64% of the patients were male and 43% of the patients had stage IV disease.

Table 1
Baseline characteristics among patients with non-small cell lung carcinoma receiving platinum chemotherapy.

Variable	No. of patients (%)
Mean age in years (SD)[a]	59.5 (±10.6)
Sex	
Male	504 (64.3)
Female	280 (35.7)
Histology	
Adenocarcinoma	350 (44.6)
Large cell	238 (30.4)
Squamous cell	192 (24.5)
Smoking habits (missing = 49)	
Current	367 (46.8)
Former	312 (39.8)
Never	56 (7.1)
ECOG performance score (missing = 57)	
0	364 (46.4)
1	312 (39.8)
2	46 (5.9)
3	3 (0.4)
4	2 (0.3)
Disease stage	
I–IIb	42 (5.4)
IIIa	197 (25.1)
IIIb	199 (25.4)
IV	346 (44.1)

[a] Standard deviation.

Table 2 shows common risk factors for the study population, comparing patients with TE during chemotherapy to those without TE. History of TE was significantly associated with TE during chemotherapy ($p < 0.01$). Risk factors for ATE such as smoking,

Table 2
Univariate analysis of risk factors for thromboembolic events (TE) among study population.

Variable	No. of patients (%)		*p* value
	TE	No TE	
History of TE			
Yes	15 (16.3)	77 (83.7)	<0.01
No	48 (6.9)	644 (93.1)	
Atrial fibrillation			
Yes	4 (11.1)	32 (88.9)	0.49
No	59 (7.9)	689 (92.1)	
Diabetes			
Yes	4 (6.8)	55 (93.2)	0.71
No	59 (8.1)	666 (91.9)	
Smoking status			
Current	27 (7.4)	340 (92.6)	0.21
Former	25 (8.0)	287 (92.0)	
Never	8 (14.3)	48 (85.7)	
Hypertension			
Yes	10 (8.5)	107 (91.5)	0.83
No	53 (7.9)	614 (92.1)	
Platinum used			
First-line			
Cisplatin	51 (7.9)	593 (92.1)	0.36
Carboplatin	5 (4.2)	113 (95.8)	
Both	2 (9.1)	20 (90.9)	
Second-line			
Cisplatin	2 (4.9)	39 (95.1)	0.92
Carboplatin	3 (6.5)	43 (93.5)	
Both	0	1 (100)	