Biomedicine & Pharmacotherapy 81 (2016) 210–217

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Prognostic value of plasma D-dimer levels in patients with small-cell lung cancer

Yi Chen[a,1], Haiming Yu[b,1], Chao Wu[b], Jinyu Li[b], Shunchang Jiao[b,*], Yi Hu[b], Haitao Tao[b], Baishou Wu[b], Aijie Li[b]

[a] Medical Center Tsinghua University, Tsinghua University, Beijing 100084, China
[b] Department of Medical Oncology, Chinese PLA General Hospital, Beijing 100853, China

ARTICLE INFO

Article history:
Received 23 October 2015
Received in revised form 15 February 2016
Accepted 15 February 2016

Keywords:
SCLC
D-dimer
Chemotherapy
Progression free survival (PFS)
Overall survival (OS)

ABSTRACT

Objective: Little data exists with respect to the relationship between the level of plasma D-dimer and prognosis of small cell lung cancer (SCLC).The aim of this study was to investigate whether the levels of plasma D-dimer could be served as a prognostic factor in patients with SCLC.
Methods: A total of 393 patients with SCLC were addressed in the present retrospective study. Plasma D-dimer levels were measured by immunoturbidimetric assay. The correlation between plasma D-dimer levels and other clinical features, progression free survival (PFS) and overall survival (OS) was analyzed statistically.
Results: The plasma D-dimer levels were significantly correlated with karnofsky performance status (KPS), tumor stage, number of metastatic sites, and treatment response. The PFS and OS of patients with elevated D-dimer levels before chemotherapy were significantly shorter than that of patients with normal D-dimer levels (PFS: 6.2 months versus 9.6 months, $P<0.001$; OS: 15.7 months versus 24.4 months, $P<0.001$). The patients with D-dimer levels converting from high to normal had better PFS and OS than those with D-dimer levels remaining high after two cycles of chemotherapy. According to multivariate analysis, elevated D-dimer level was confirmed to be an independent prognostic factor for worse survival.
Conclusions: Elevated plasma D-dimer level could be served as an independent determinant of poor prognosis in patients with SCLC.

1. Introduction

Activation of coagulation and fibrinolysis is found to be frequently related with most malignancies [1], although the mechanism involved remains to be not completely clarified. Interestingly, such activation in haemostatic system can be observed in many cancer patients, even without presence of venous thromboembolism (VTE) [2,3]. It has been reported that the extent of coagulation activation is associated with angiogenesis, tumor cell invasion, tumor progression and prognosis in many cancers [1,4–8], comprising lung cancer, gastrointestinal cancer and breast cancer. Activation occurs in two main methods, either resulting in coagulation through thrombin formation or activation of fibrinolytic system through plasmin [9,10]. Patients with cancer and hypercoagulation have a high risk of venous thromboisi and a poor prognosis. Moreover, some increased or decreased coagulation factors contribute to cancer growth and metastasis.

D-dimer, as a end-product of fibrin degradation, levels of which are elevated by increasing fibrin formation and fibrinolysis, is a widely used biomarker indicating the activation of coagulation and fibrinolysis, therefore it is routinely used in combination with other biochemical factors in the assessment of potential thrombotic episodes (e.g. VTE). The measurement of D-dimer is routinely used in conjunction with clinical parameters in the assessment of suspected acute VTE. Besides, elevated D-dimer level is also observed in other clinical settings and can predict the occurrence of VTE in cancer patients. Previous reports have showed that increasing plasma D-dimer levels were correlated with poor prognosis of patients with many solid tumors, including lung cancer [4,11–14]. However, almost all these studies include both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) patients, therefore the results may

* Corresponding author at: Department of Medical Oncology, Chinese PLA General Hospital, Fuxing Road 28, Haidian District, Beijing 100853, China.
E-mail address: changjiao84@126.com (S. Jiao).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.biopha.2016.02.030
0753-3322/

be influenced due to the heterogeneity of treatment response and natural disease course between NSCLC and SCLC. The data with respect to the relationship between D-dimer levels and prognosis of SCLC is still lacking.

The purpose of the present study was to investigate the correlation between plasma D-dimer levels and clinical features as well as to analyze the prognostic value of plasma D-dimer in patients with SCLC. The outcomes of our study might help predict the progression of SCLC and provide potential treatment for further research.

2. Patients and methods

2.1. Patients

From medical information database of Chinese PLA General Hospital, 393 patients with pathologically or cytologically confirmed SCLC were selected during June 2004–May 2014 and during the same time period, 100 healthy individuals receiving routine physical examination in our hospital were enrolled as control group. This retrospective study was approved by the Ethics Committee of Chinese PLA General Hospital and all written informed consents of participants were provided before treatment.

2.2. Inclusion and exclusion criteria

The main inclusion criteria: (1) pathologically or cytologically proven SCLC; (2) KPS $\geq$ 70; (3) age $\geq$ 18 years; (4) adequate hematological reserves (white blood cell counts $\geq 4 \times 10^9$/ml; granulocyte counts $\geq 1.5 \times 10^9$/ml; platelet counts $\geq 100 \times 10^9$/ml); (5) adequate hepatic [total serum bilirubicin concentration $\leq$1.5 times the upper limit normal (ULN); serum transaminases and alkaline phosphatase $\leq$2.5ULN, when liver metastases were present at baseline by radiographic images, the patient was eligible unless these levels were >5 ULN] and renal function (serum creatinine concentration <1.5 ULN and creatinine clearance >50 ml/min); (6) complete follow-up data. The exclusion criteria: (1) NSCLC or combined-type SCLC; (2) evidence of other active malignant disease; (3) patients with myocardial infarction, arterial or venous thromboembolism within 3 months before treatment; (4) patient with either anticoagulant or anti-aggregate therapies; (5) patients with active infectious disease, trauma, stroke and severe wounds; (6) pregnancy and lactation; (7) patients who received surgical resection of primary tumor.

2.3. Performance status, diagnosis, staging and treatment response

Performance status was assessed according to KPS scale. The diagnosis of SCLC was determined by the outcomes of bronchofiberoscopy, mediastinoscopy, percutaneous lung biopsy or lymph node biopsy in combination with computed tomography (CT) scan, magnetic resonance imaging (MRI), ultrasonography of abdomen, bone scan and positron emission tomography (PET-CT). The staging of the patients was based on the U.S. Veterans Administration Lung Cancer Group. The stages of the patients were classified into two categories: 1) limited disease (LD), which referred to the disease confined to ipsilateral hemithorax and safely encompassed within a radiation field; 2) extensive disease (ED), which referred to the disease beyond ipsilateral hemithorax, including malignant pericardial or pleural effusion or hematogenous metastasis. Treatment response was estimated according to the evaluation criteria in solid tumor (RECIST) at the first imaging evaluation (before the third cycle of chemotherapy). The treatment response included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

2.4. Treatment

267 (67.9%) patients received chemotherapy in combination with radiotherapy (including thoracic radiotherapy and brain radiotherapy) and 126 (32.1%) received chemotherapy only. The majority (382 patients) were treated with platinum-based chemotherapy regimens: cisplatin or carboplatin combined with etoposide or irinotecan. In patients with limited-stage SCLC (n = 157, 39.9%), 49 patients were treated by thoracic concurrent radiochemotherapy and 70 received sequential radiochemotherapy. In patients with extensive-stage SCLC (n = 233, 59.3%), 39 patients received thoracic concurrent radiochemotherapy and 86 patients received sequential radiochemotherapy. Among limited-stage SCLC patients, 38 patients were treated with prophylactic cranial irradiation (PCI) and 24 with therapeutic brain radiotherapy after brain metastasis. 24 patients with extensive-stage SCLC were treated with PCI and 49 with therapeutic brain radiotherapy. For patients who were evaluated as PD after 2 cycles of chemotherapy, second-line chemotherapy with or without radiotherapy were given according to the NCCN guidelines for SCLC.

2.5. Follow-up

In our study, PFS was defined as the time from the date of first cycle of chemotherapy to the date of progression or death or patient censoring at the last follow-up. OS was defined as the time from the date of first cycle of chemotherapy to the date of death or patient censoring at the last follow-up.

Treatment response was assessed every 6 weeks during treatment. After recovery from primary therapy, patients were evaluated every 3 months in our hospital. The median follow-up period was 12 months (range: 3 months-108 months). All the information collected was recorded in a database for the following analysis.

2.6. Measurement of plasma D-dimer, lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA)

5 mL venous blood were extracted from the patients with SCLC and plasma was isolated by centrifugation. Plasma D-dimer levels were measured by immunoturbidimetric assay [STA-R EVOLUTION® EXPERT SERIES (QWERTY KEYBOARD), Stago, France]. The normal level of plasma D-dimer was $\leq$0.5 μg/mL, hence plasma D-dimer level of >0.5 μg/mL was defined as elevation. The plasma D-dimer levels before chemotherapy and after two cycles of chemotherapy were measured. Levels of lactate dehydrogenase (LDH) and Carcinoembryonic Antigen (CEA) before chemotherapy were also measured. The serum level of CEA was measured by electrochemiluminescence immunoassay (MODULAR ANALYTICS C270, Roche Diagnostics, Germany) and the serum level of LDH was measured by enzyme dynamic method (MODULAR ANALYTICS C270, Roche Diagnostics, Germany). The normal upper limit of serum LDH and CEA was 250U/L and 5ug/L, respectively, according to the recommended values from the corresponding manufacturers.

2.7. Statistical analysis

The patients' characteristics were described by median values and inter-quartile range (Q1-Q3) due to non-normal distribution of the continuous variables. Categorical variables were compared by Chi-square test or Fisher' exact test, and continuous variables in different subgroups were compared by Mann–Whitney U test. Survival curves were generated by Kaplan–Meier method; univariate analysis and multivariate analysis were performed by