The correlation between hemostatic parameters and mortality rate in patients with non-small cell lung cancer

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Abstract

The increasing level of hemostatic parameters and tumor markers were associated with cancer progression and poor prognosis, particularly in NSCLC. The objective of this study is to determine whether there was a correlation between hemostatic parameters and mortality rate in patients with NSCLC. This was a prospective analytical study with a pretest-posttest design which included 41 patients with diagnosis of NSCLC. Plasma levels of PT, APTT, TT, D-dimer, and fibrinogen were measured before initiation of chemotherapy and re-measured after 4 cycles or 6 cycles of chemotherapy, based on the clinical condition of patients. Then, patients were followed up for 1 year to evaluate the mortality rate. The majority of subjects were male (85.4%) with adenocarcinoma (75.6%). There was no significant difference in mean between adenocarcinoma and squamous cell carcinoma (P>0.05). Most patients died after one month of follow up (61%). The parameters which could predict high mortality rate in NSCLC were prolonged PT and the increased of D-dimer with RR>1, although they had not significant in statistical analysis (P>0.05). There is no correlation between hemostatic parameters and mortality rate in patients with NSCLC.

Materials and Methods

This was a prospective analytical study with one group posttest-pretest design that held in Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara for 17 months in 2015-2016. This study protocol was approved by the Ethics Committee of Faculty of Medicine in Universitas Sumatera Utara.

Patients

This study included 41 participants with non-small cell lung cancer. Diagnosis was made by history taking, physical examination, and work-up examinations such as chest X-ray, chest computed-tomography with contrast, and then confirmed by biopsy and cytology taken at bronchoscopy. Patients who had coagulation disorder, in taking anti-coagulant medications, or had other malignancies beside lung cancer were excluded. Smoking history was based on medical records and categorized as active smoker and non-smoker. Active smoker was patients who had consumed ≥100 cigarettes per years. Before taking chemotherapy, all participants got an initial examination such as performance status by WHO classifications, liver function test, renal function test, and hemostatic parameters. These tests were examined 7 days before chemotherapy procedure. One cycle of chemotherapy lasted 21 days. Then, second examinations were done after fourth cycle of chemotherapy (4th month) and after the end of first-line chemotherapy (6th month).

Blood collection

A blood sample was obtained by peripheral venous puncture and collected in a tube containing EDTA for anti-coagulant. Prothrombin (PT), Activated Partial Thromboplastin Time (APTT), Thrombin Time (TT) were analyzed using Coatron A4 with photo optic and electromechanics. Fibrinogen was analyzed using Coatron A4 with optic LED laser. D-dimer was analyzed using Coatron A4 with immunoturbidimetric assay.

Statistical analysis

All these data were analyzed using Epi
Results

Table of 41 participants included in this study age ≥ 40 years old with the diagnosis of NSCLC. From Table 1, we can see that the majority of the subject is male, smoker, in 50-59 age groups with type of cancer was adenocarcinoma. Most patients have received gemcitabine as drug of choice of their chemotherapy. General characteristics of this study can be seen in Table 1.

Table 1. General characteristics of participants.

| Characteristics          | N   | %    |
|--------------------------|-----|------|
| Age                      |     |      |
| 40-49                    | 7   | 17.1 |
| 50-59                    | 20  | 48.8 |
| ≥= 60                    | 14  | 34.1 |
| Sex                      |     |      |
| Male                     | 35  | 85.4 |
| Female                   | 6   | 14.6 |
| Histopathology           |     |      |
| squamous cell ca         | 10  | 24.4 |
| Adenocarcinoma           | 31  | 75.6 |
| Stage                    |     |      |
| I-IIB                    | 3   | 7.3  |
| IIIa-IIIb                | 15  | 36.6 |
| IV                       | 23  | 56.1 |
| Smoking history          |     |      |
| Smoker                   | 35  | 85.4 |
| Nonsmoker                | 6   | 14.6 |
| History of chemotherapy  |     |      |
| Paclitaxel               | 10  | 24.4 |
| Gemcitabine              | 27  | 65.9 |
| Vinorelbine              | 4   | 9.5  |
| One month follow up post chemotherapy |   |      |
| None                     | 2   | 4.9  |
| Motric disably           | 14  | 34.1 |
| Death                    | 25  | 61.0 |
| One year follow up post chemotherapy | | |
| None                     | 2   | 4.9  |
| Motric disably           | 3   | 7.3  |
| Death                    | 36  | 87.8 |
| Total                    | 41  | 100  |

After 1 month and 1 year follow up, hemostatic parameters were assessed in participants who survived. Hemostatic parameters and tumor marker were categorized as normal and abnormal. The cutting of points on abnormal level were PT>14 s, APTT>30 s, TT>14 s, D-dimer >375 ug/l, CEA>5 IU, NSE>17 IU, Cyfra >10 IU. From Table 4 we could see the parameters which could predict poor prognosis in NSCLC were prolonged PT, the increased of D-dimer, and CEA with RR>1, although they had not significant in statistical method using logistic regression (P>0.05). The increase of NSE (>17 IU) was significant to predict 1-year survival rate of patients with NSCLC.

Discussion

Lung cancer is one of the common malignancy in both women and men which has a poor prognosis. These made many studies concern on searching for predictors on survival rate of lung cancer, such as tumor staging, genetic factors, tumor markers, inflammatory markers, and hemostatic parameters. In lung cancer, these prognostic factors are useful in understanding the course of disease, choosing alternative treatment, and educating the patients.

Recent years, a number of studies have revealed basic hemostatic parameters such as platelet, PT, APTT, D-dimer, AT-III increased in lung cancer. Almost 90% advanced stage cancer has coagulation factor abnormalities, including prolonged and
various solid tumor malignancy. Ruiz mustard analogs have an association with endothelial damage and increase tissue fac-
chemotherapy, anthracyclines, and nitrogen in various solid cancer. Chemotherapy of the hypotheses that explains this phe-
higher than without chemotherapy. The chemotherapy was poorly understood. Oneject had adenocarcinoma (Table 1). This is the other hand, NSCLC activates coagula-
cancer (Table 2). This is in line with Unsal study that showed there was no significant differences in PLT, PT, APTT, fibrinogen,
carcinoma and squamous cell carcinoma lung cancer (Table 2). This is in line with Unsal study that showed there was no significant differences in PLT, PT, APTT, fibrinogen, AT-III, and fibrinogen among histology of lung cancer.10
Hemostatic parameters as prognostic indicators of NSCLC remain controversial. Many studies showed a strong correlation between hemostatic parameters and cancer progression in line with poor prognosis.1,3 In this study, we found that prolonged PT and the increasing level of D-dimer had increased mortality rate although it was not significantly correlated in statistical analysis. Buccheri study showed PT was a signif-
cancer that showed a higher risk of VTE in adenocarcinoma rather than squamous cell carcinoma in NSCLC.16,23 But in this study, there were no significant differences in hemostatic parameters between adenocarcinoma and squamous cell carcinoma lung cancer. This is in line with Unsal study that showed an increase in TT and INR in NSCLC patients but they were not significantly correlated. This is in contrast with Tas study that found a significant correlation between TT and INR with poor prognosis and short survival in lung cancer.27

Conclusions
There is no correlation between hemo-
static parameters and mortality rate in patients with NSCLC.

Table 3. One year follow up of NSCLC.
| Survival rate | N  | % |
|---------------|----|---|
| Baseline      | 41 | 100 |
| 1 month follow up | 16 | 39.0 |
| 1-year survival | 5  | 12.2 |

Table 4. Prognostic role of hemostatic parameters and tumor marker.
|                      | 1-month survival |  | 1-year survival |  |
|----------------------|------------------|---|------------------|---|
|                      | RR               | P-level | RR               | P-level |
| PT >14 s             | 2.03             | 0.35    | 1.53             | 0.71 |
| aPTT >30 s           | 0.90             | 0.98    | 0.83             | 0.85 |
| TT >14 s             | 0.71             | 0.61    | 5.01             | 0.18 |
| INR <1.0             | 0.35             | 0.63    | 0.35             | 0.63 |
| D dimer >375         | 1.06             | 0.92    | 1.17             | 0.86 |

*P level considered significant in logistic regression.

shortened PT and APTT, increased and decreased intrinsic or extrinsic coagulation factors, increased fibrinogen and other fibrin degradation products such as D-dimer, and simple predictors such as increase of platelet count. Lung cancer was divided into 2 groups based on type of cell, NSCLC, and SCLC. These groups have different mechanisms for activating coagulation cascade. In SCLC, tumor cells directly activating coagulation cascade by releasing tissue factor. In the other hand, NSCLC activates coagulation cascade by host macrophage system. Based on histopathology, NSCLC was divided into adenocarcinoma, squamous cell carcinoma, large cell carcinoma (undifferentiated), and other subtypes such as adenosquamous carcinoma, etc. In this study, we can see that the majority of subject had adenocarcinoma (Table 1). This is in line with Soeroso et al that found the most common NSCLC was adenocarcinoma (80.9%).
Along with the course of disease, chemotherapy also increases hypercoagula-
ble state risk, depending on duration and particular agents. Platinum-based chemotherapy, anthracyclines, and nitrogen mustard analogs have an association with venous thromboembolism (VTE) state in various solid tumor malignancy. Ruiz and Ferigno et al. showed increasing hemostatic parameters after chemotherapy in various solid cancer. Chemotherapy can increase the risk of VTE until 6-8 fold higher than without chemotherapy. The mechanism of thromboembolic event after chemotherapy was poorly understood. One of the hypotheses that explains this phe-
omena is chemotherapy, particularly cisplatin-based therapy can directly induce endothelial damage and increase tissue fac-
tor procoagulant activity of macrophages. Other factors contributing this are cytokine release by apoptosis of tumor and endothelial cells that later increase tissue factors which enhance hypercoagulable state.
The site of cancer is one of the risk factors of VTE in malignancy. Whereas, the highest incidence of VTE is associated with pancreatic tumor, lung, GI tract, and brain tumor. Another factor is histology of cancer that showed a higher risk of VTE in adenocarcinoma rather than squamous cell carcinoma in NSCLC. But in this study, there were no significant differences in hemostatic parameters between adenocarcinoma and squamous cell carcinoma lung cancer. Other factors contributing this are cytokine release by apoptosis of tumor and endothelial cells that later increase tissue factors which enhance hypercoagulable state.

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Article

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