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Clinical and prognostic significance of plasma fibrinogen in lung cancer

Chen YS[1,2,*], Zeng DH[1], Li HR[1,2], Wu YL[1], Lin X[1], Xu NL[1,2] and Lin M[1,2]

[1] Fujian Provincial Clinical Medical College, Fujian Medical University, Fuzhou, Fujian, 350001, P.R. China
[2] Department of Respiratory Medicine, Fujian Provincial Hospital, Fuzhou, Fujian, 350001, P.R. China

Abstract

Objectives: Hyperfibrinogenemia is a common problem associated with various carcinomas. The recent studies have shown that high plasma fibrinogen concentration is associated with invasion, growth and metastases of cancer. Furthermore, the recent studies focus on the prognostic significance of fibrinogen in the patients with advanced NSCLC (stage IIIB -IV). However, the prognostic significance of the plasma fibrinogen levels in early stage NSCLC patients (stage I -IIIA) still remains unclear. In addition, it remains unclear whether or not chemotherapy-induced changes in fibrinogen level relate to the prognosis. The aims of this study were to 1) further explore the relationship between the plasma fibrinogen concentration and the stage and metastases of lung cancer 2) evaluate the prognostic significance of the basal plasma fibrinogen level in patients with lung cancer 3) explore the prognostic value of the change in fibrinogen levels between pre and post-chemotherapy. *Methods:* In this retrospective study, the data from 370 patients with lung cancer were enrolled into this study. The plasma fibrinogen levels were compared with the clinical and prognostic significance of lung cancer. The association between the plasma fibrinogen level and clinical-prognostic characteristics were analyzed using SPSS 17.0 software. *Results:* 1) The median pre-treatment plasma fibrinogen levels were 4.20g/L. Pre-treatment plasma fibrinogen levels correlated significantly with gender ($p = 0.013$). A higher plasma fibrinogen concentration was associated with squamous cell carcinoma versus adenocarcinoma (4.83 ± 1.50 g/L versus 4.15 ± 1.30 g/L; $P < 0.001$), there was a significant association between plasma fibrinogen level and metastases of lung cancer, pointing a higher plasma fibrinogen level in lymph nodes or distant organ metastases ($p < 0.001$). 2) Patients with low plasma fibrinogen concentration demonstrates higher overall survival compared with those with high plasma fibrinogen concentration (median, 19 months versus 35 months; $P < 0.001$). In addition, a similar result was observed in 194 early stage NSCLC (stage I -IIIA) ($P < 0.001$). Univariate and multivariate analysis revealed that higher levels of fibrinogen (FIB≥4.20 g/L), age, distant metastases and pathological types were positively associated with shorter overall survival (OS). 3) In addition, there was a significant link between the elevation by more than 15% in the plasma fibrinogen level after receiving short-term chemotherapy and shorter overall survival (OS). *Conclusion:* 1) This study shows high plasma fibrinogen concentration is associated with lymph nodes or distant organ metastases in lung cancer. 2) Furthermore, our results indicate a significant relevance between high pre-treatment plasma fibrinogen concentration and poor prognosis in patients with lung cancer. 3) In addition, we find that the patients with a low plasma fibrinogen level will have a shorter OS if the plasma fibrinogen level increases significantly after receiving short-term chemotherapy. Interestingly, we also find that the patients with a high plasma fibrinogen level will have a longer OS if the plasma fibrinogen level decreases significantly after receiving short-term chemotherapy, which indicate the change of the plasma fibrinogen level after receiving short-term chemotherapy may be used as an independent prognostic factor.

Keywords: lung cancer; fibrinogen; overall survival; prognosis; cancer stage; short-term chemotherapy

Introduction

Patients with malignant tumour often have systemic blood coagulation dysfunction, the relationship between cancer and coagulation is characterized by several mechanisms pointing that tumour biology and coagulation are closely linked processes [1]. The recent studies have indicated that cancer induced hemostatic activity promoted tumour growth and tumour cell dissemination [2]. For instance, activating coagulation system is supposed to behave more aggressively with higher risk of invasion and metastases in patients with cancer. The specific relationship between

*Corresponding author: Yu-sheng Chen, Department of Respiratory Medicine, Fujian Provincial Hospital No.134 East Street, Gulou District, Fuzhou, Fujian, 350001, P.R. China. Tel.: +86-591-87557768-1023; Fax: +86-591-87609181; E-mail: chenyushengfjsl@163.com

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coagulation parameters and malignancy has been shown to be associated with decreased survival for several tumour types in previous studies [3−11].

Fibrinogen as one of the important coagulation parameters is synthesized effectively in the liver and can be converted to fibrin by thrombin during the coagulation cascade. High expression of fibrinogen is often observed in lung cancer patients with local regional or distant metastasis. However, the clinical studies have produced conflicting results about the prognosis of the plasma fibrinogen level in lung cancer patients. A recent study found basal plasma fibrinogen level could be used as an independent prognostic parameter for the OS of advanced NSCLC through the study of 160 patients [12]. However, another research found that high plasma fibrinogen level was associated with decreased survival in patients but not reach statistically significant difference through the study of 110 lung cancer patients, which indicated that fibrinogen could not be used as a useful marker for the prognosis [13]. Furthermore, there are few researches about the relationship between the prognostic significance of fibrinogen and NSCLC (stage I-IIIA). So the relationship between the plasma fibrinogen level and prognosis of patients with lung cancer still remains unclear and disputed. In addition, current clinical researches have showed that the reduction in plasma fibrinogen levels induced by chemotherapy might be used for evaluating the efficacy of chemotherapy in advanced NSCLC [12]. However, it remains unclear whether or not chemotherapy-induced changes in fibrinogen level relate to the prognosis.

The purposes of this study were to: a) further explore the relationship between the pre-treatment fibrinogen levels and the clinical and prognostic significance of lung cancer; b) investigate the relationship between the change of the plasma fibrinogen level after short-term chemotherapy and overall survival.

Materials and methods

Patient selection

We analyzed patients with lung cancer who had been enrolled between January 2009 and August 2012 at the Fujian Provincial Hospital of China (Fujian, China). The approval from the Institutional Review Board was obtained for this study. Between that period, a total of 797 patients with histologically or cytologically confirmed non small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) were detected in our hospital. All of the enrolled patients in this study were newly confirmed without previous treatment. Patients with following characteristics were excluded from the study: 1) had not been tested for fibrinogen levels before treatment; 2) had adequate hepatic, renal, hematologic and cardiac function, severe acute or chronic inflammatory diseases, coagulation disturbances, chronic liver diseases, chronic renal failure or oral anticoagulation therapy; 3) patients who did not undergo systemic imaging studies including CT scan-chest, brain imaging's, the whole body bone ECT, abdominal sufficiency or whole body PET-CT examination. Four hundred and twenty seven patients were excluded by these criteria, and finally, a total of 370 patients were eligible for the study.

The median age of excluded group is 59.0 (range, 21-85), the ratio between the male and female patients of the excluded group is 78.6%:21.4%. And the ratio of histological type of excluded group has been shown that small cell lung cancer: squamous carcinoma: adenocarcinoma: other type is 11.0%:23.2%:50.4%:15.4%. Furthermore, the distribution of age ($p=0.113$), gender ($p=0.441$), and histological type ($p=0.589$) was not statistically different between enrolled and excluded patients. The 370 patients were followed up on February 5, 2013. At closure of the study, dead or alive status was recorded for all patients. One hundred and eighty patients had died by the cutoff date.

Detection of serum fibrinogen

The STA Fibrinogen Kit is intended for the quantitative determination of the fibrinogen level in blood plasma using the Clauss clotting method. The reference range of plasma fibrinogen level was defined as being between 2 and 4 g/L using this method.

Statistical analyses

All statistical analyses in this study were carried out using the SPSS 17.0 statistical package for Windows. The continuous data was expressed as the mean ± standard deviation and the categorical data was expressed as percentages (%). The relationship between the plasma fibrinogen concentration and clinicopathological factors was evaluated using Mann–Whitney U test, Kruskal-Wallis test, the two independent sample "t" tests or the Spearman rank correlation coefficient where appropriate. Receiver operating curve (ROC) analysis was used to determine potential cutoff values of fibrinogen for prediction of lymph nodes or distant organ metastases. The Kaplan-Meier curve was used to describe OS, and differences between groups were compared by means of the log-rank test. Univariate analysis comprised sex (male vs. female), age (≤60 years vs. >60 years), histological type (small cell lung cancer vs. adenocarcinoma vs. squamous cell carcinoma vs. other pathological types), cancer stage (node or distant organ metastases vs. no metastases) and pre-treatment fibrinogen levels (<4.20 g/L vs. ≥4.20g/L). All statistical analysis parameters presenting significant correlation or a tendency towards association ($P<0.20$) with the outcomes of interest were entered into multivariable logistic regression analysis. Results were analyzed for the end points of OS. A P value <0.05 was considered as being statistically significant in all statistical analyses.

Results

Correlation analysis

The mean (±SD) pre-treatment plasma fibrinogen level was 4.51±1.62 g/L in the 370 patients. Ages ranged between 21 and 85 years, with a median age of 59 years. In addition, we also select 139 healthy persons as a control group. The mean (±SD) pre-treatment plasma fibrinogen concentration is 2.83±0.39g/L. Ages ranged between 38 and 78 years, with a median age of 58 years. The comparison between healthy persons and lung cancer patients is shown in table1.

Table 1 Comparison between healthy persons and patients with lung cancer

	The plasma fibrinogen level	N	P value
Patients	4.51±1.62 g/L	370	<0.001
Healthy persons	2.83±0.39g/L	139	

The clinicopathological parameters evaluated including sex, age, histological type, cancer stage and the pre-treatment plasma fibrinogen level. Correlations between pre-treatment plasma fibrinogen levels and clinicopathological parameters are presented in Table 2. The difference of plasma fibrinogen concentration including sex, age, metastases, lung cancer stage, distant organ metastases, brain metastases, bone metastases is compared by independent samples "t" tests. Furthermore, the comparison of histological type is used one-way ANOVA test (Appendix). High plasma fibrinogen levels were associated with sex ($P = 0.013$), cancer stage ($P = 0.001$), distant organ metastases ($P = 0.039$), histological type ($P < 0.001$). Patients with nodes or distant organ metastases had higher pre-treatment plasma fibrinogen levels ($P < 0.001$).

Spearman rank correlation coefficient analysis also revealed a significant correlation between the fibrinogen

Table 2 Correlation between pre-treatment plasma fibrinogen levels and clinicopathological parameters

Variable		*Number of patients (%)*	*Fibrinogen levels (g/L)*	*P value*
Sex				0.013
	Male	26 (70.8%)	4.64±1.63	
	Famale	108 (29.2%)	4.18±1.56	
Age				0.937
	>60	206 (55.7%)	4.50±1.50	
	≤60	164 (44.3%)	4.51±1.71	
Histological type				
	Small cell carcinoma	33 (8.9%)	4.47±1.52	<0.001
	Squamous carcinoma	90 (24.3%)	4.83±1.50	
	Adenocarcinoma	180 (48.6%)	4.15±1.30	
	Others	67 (18.1%)	5.06±2.27	
Metastases				
	node or distant organ metastases	302 (81.6%)	4.67±1.63	<0.001
	no metastases	68 (18.4%)	3. 81±1.38	
Stage of disease Non-small cell lung cancer				<0.001
	Local (stage I -IIIA)	194 (57.6%)	4. 26±1.68	
	Local (stage IIIB-IV)	143 (42.4 %)	4.86±1.49	
Small cell lung cancer				0.57
	Limited	11 (33.3%)	4.27±1.21	
	Extensive	22 (66.7%)	4.57±1.68	
Distant metastases				0.039
	Distant metastases	165 (44.6%)	4.70±1.50	
	no metastases	205 (55.4%)	4.35±1.70	
Brain metastases				0.614
	metastases	317 (85.7%)	4.52±1.68	
	no metastases	53 (14.3%)	4.42±1.23	
Bone metastases				0.508
	metastases	113 (30.5%)	4.62±1.51	
	no metastases	257 (14.3%)	4.46±1.66	

level, white blood cell (WBC) count, platelet count. Higher plasma fibrinogen level was often observed to be significantly correlated with increased WBC (R2 = 0.331; P < 0.001),) and platelet counts (R2 = 0.493; P < 0.001), The data comparing fibrinogen with white blood cell count and platelet count has been shown and demonstrated in table 3.

Table 3 The data comparing fibrinogen with white blood cell count and platelet count

	Fibrinogen	white blood cell count	platelet count
Mean±SD	4.51±1.62	8.15±2.74	277.48±88.75
Fibrinogen correlations	1.000	0.331 (P<0.001)	0.493(P<0.001)

Cut off fibrinogen values from ROC analysis and ROC analysis of serum fibrinogen to predict lymph nodes or distant organ metastases are shown in Figure 1, respectively. For screening method, serum fibrinogen value of 3.65 g/L seemed to be the appropriate cut off level for the prediction of lymph nodes or distant organ metastases with 69.2% of sensitivity, 57.4% of specificity. The area under the ROC was 0.671 (p<0.001, 95% confidence interval of 0.599–0.743), which indicates the potential predictive value of node or distant organ metastases.

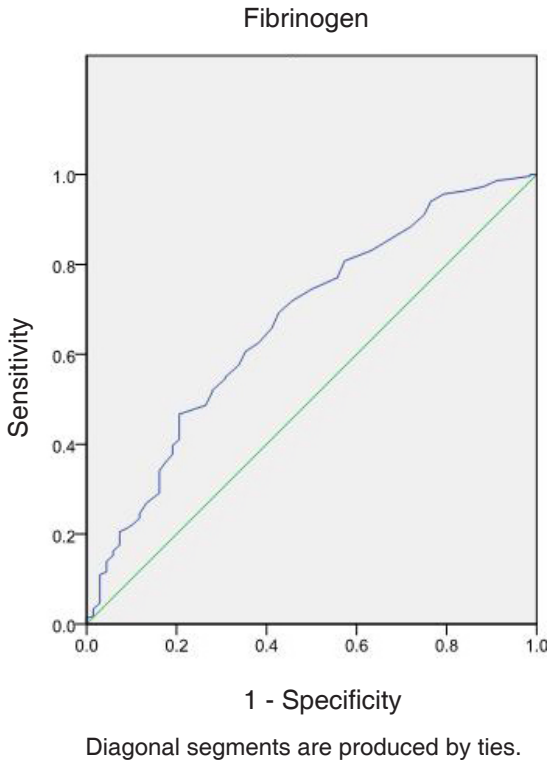

Figure 1 ROC analysis of serum fibrinogen to predict lymph nodes or distant organ metastases

Pre-treatment plasma fibrinogen levels and prognosis

In order to evaluate the value of pre-treatment fibrinogen level as a prognostic factor, the relationship between the plasma fibrinogen level and OS was analyzed. Patients were divided into two groups, one above and the other below the median pre-treatment plasma fibrinogen level of 4.20 g/L. The data showed that patients with hyperfibrinogen had a shorter OS than those with lower plasma fibrinogen level (Figure 2; p <0.001). Furthermore, we evaluated the prognostic value of fibrinogen levels in NSCLC (stage I -IIIA). Patients were divided into two groups, one above and the other below the median pre-treatment plasma fibrinogen level of 3.80 g/L in 194 patients with NSCLC (I-IIIA). The data also showed that patients with hyperfibrinogen had a shorter OS than those without hyperfibrinogen (Figure 3; p<0.001).

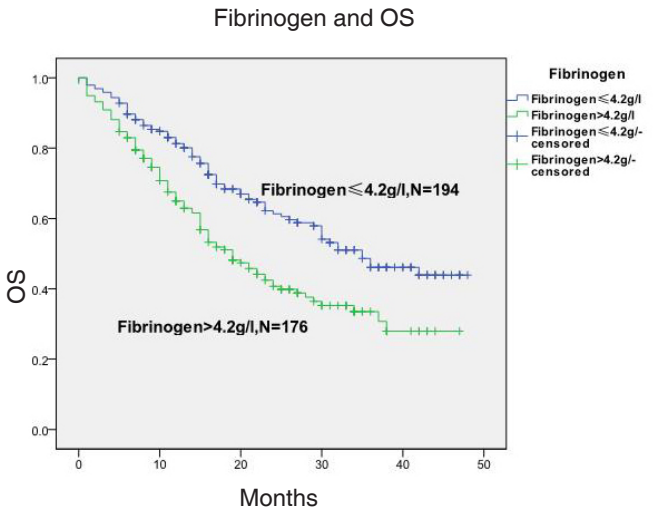

Figure 2 Kaplan–Meier curves for overall survival (OS) broken down by median plasma fibrinogen level (4.2 g/L) in 370 patients. p < 0.001.

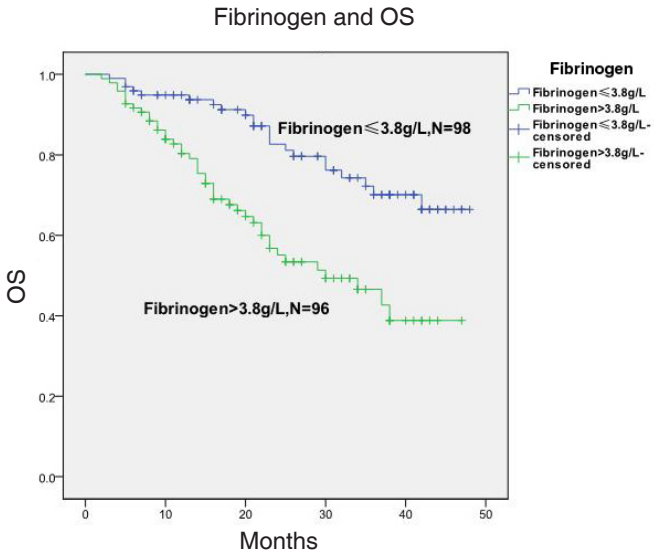

Figure 3 Kaplan–Meier curves for overall survival (OS) had broken down by median plasma fibrinogen level (3.80 g/L) in 194 NSCLC (stage I -IIIA) patients. p < 0.001.

In the univariate analysis, the significant prognostic factors were age (P=0.007), histological type (P=0.002),

cancer stage (P<0.001), pre-treatment plasma fibrinogen levels (P<0.001), as shown in Table 4. Furthermore, multivariate analysis also indicated that age, histological type, cancer stage, pre-treatment plasma fibrinogen levels were independent predictors of OS as shown in Table 5.

Table 4 Univariate analyses of prognostic valuables for overall survival

Characteristic	*Median Survival (month) (95%CI)*	*P Value*
Age		0.007
≤60	30.00 (21.48-38.52)	
>60	20.00 (24.32-25.67)	
Histological type		0.002
Small cell carcinoma	13.00 (10.48-15.52)	
Squamous carcinoma	23.00 (15.77-30.23)	
Adenocarcinoma	30.00 (23.49-36.51)	
Others	35.00 (not reached)	
Metastases		<0.001
node or distant	21.00 (17.618-24.382)	
Organ metastases		
no metastases	not reached	
Fibrinogen		<0.001
FIB>4.2g/l	19.00 (14.62-23.39)	
FIB≤4.2g/l	35.00 (26.88-43.12)	

Table 5 Multivariate analysis of prognostic valuables for overall survival

Characteristic	P Value	Relative risk (95%CI)
Age	0.007	1.507 (1.121-2.026)
Node or distant		
Organ metastases	0.000	4.954 (2.672-9.184)
Histological type		
Small cell carcinoma	0.004	2.237 (1.290-3.878)
Squamous carcinoma	0.494	1.174 (0.742-1.858)
Adenocarcinoma	0.708	1.084 (0.709-1.658)
Fibrinogen	0.017	1.497 (1.115-2.008)

The change of fibrinogen after chemotherapy and prognosis

Furthermore, we evaluate the prognostic value of the change in fibrinogen levels between pre and post-chemotherapy. There were 56 patients who tested fibrinogen after receiving two courses of chemotherapy in this study. All patients received platinum based chemotherapy according to the severity of their respective conditions. The patients were divided into two groups according to the change of pre and post-chemotherapy plasma fibrinogen levels (increased level group and decreased level group after receiving chemotherapy; cut off value $\Delta f = 0$ g/L). OS was not significantly different between the increased group and the decreased group (Figure 4; P>0.05). The data of overall survival between the two groups was shown in Table 6. Furthermore, we also investigated whether the condition of fibrinogen levels increased significantly after short-term chemotherapy could be a useful prognostic factor. Fifty six patients were divided into three groups according to the change in pre and post-treatment fibrinogen levels (increased level group, stable group and decreased level group after treatment; cut off value $\Delta f = 15\%$). The age, histological type and cancer stage between the three groups do not reach the statistically significant difference. However, the pre-chemotherapy plasma fibrinogen level has a significant difference between the three groups (Table 7; P<0.001). Univariate analyses indicate that the condition that the plasma fibrinogen levels increase by more than 15% after short-term chemotherapy is associated with a shorter OS (Figure 5; $p = 0.002$). The data of overall survival between the three groups is shown in Table 8. Furthermore, Cox regression analysis also show that the plasma fibrinogen levels increase by more than 15% after short-term chemotherapy may be a useful prognostic factor for lung cancer patients.

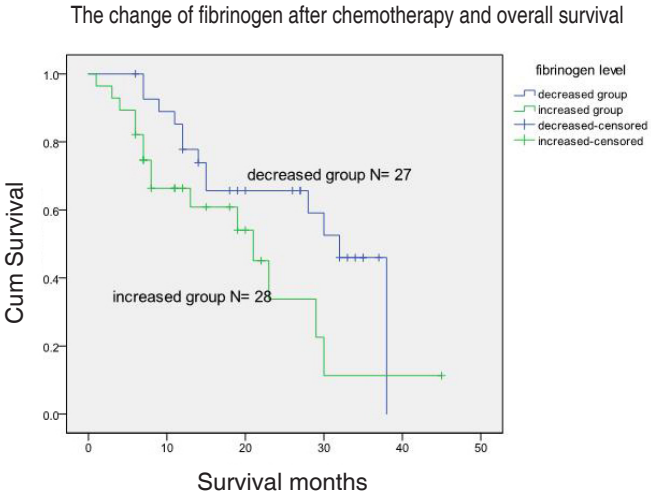

Figure 4 Kaplan–Meier curves for overall survival (OS) and the change of fibrinogen after chemotherapy in 56 patients ($\Delta f = 0$. p = 0.062).

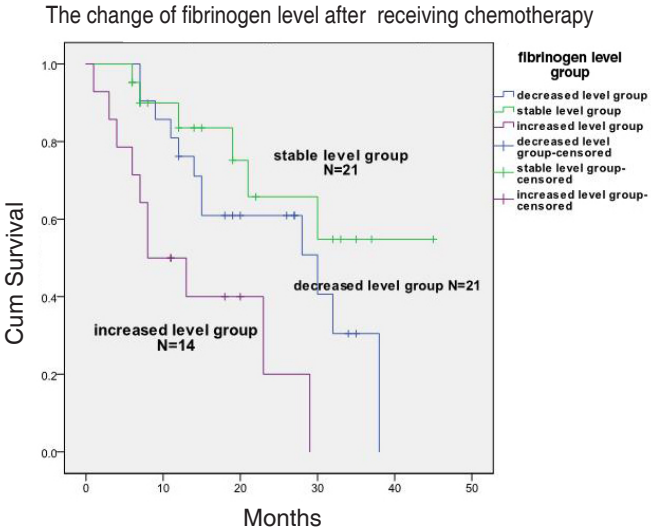

Figure 5 Kaplan–Meier curves for overall survival (OS) and the change of fibrinogen after chemotherapy in 56 patients. ($\Delta f = 15\%$. p = 0.002)

Table 6 Overall survivals of increased level group and decreased level group

Group	*Median survival (month) (95%CI)*	*P Value*
increased level group	21.00 (12.11-29.89)	0.062
decreased level group	32.00 (28.17-35.83)	

Table 7 Pre-chemotherapy fibrinogen and post-chemotherapy fibrinogen level between three groups

Groups	*Pre-chemotherapy fibrinogen levels*	*Post-chemotherapy fibrinogen levels*	*N*
increased level group	3.41±0.73	4.60±1.34	14
stable level group	4.21±1.16	4.23±0.98	21
decreased level group	5.82±2.05	3.94±1.40	21

Table 8 Overall survivals of increased level group and stable level group and decreased level group

Group	*Median survival (month) (95%CI)*	*P Value*
increased level group	8.00 (1.53-14.48)	0.002
stable level group	not reached	
decreased level group	30.00 (10.07-49.93)	

Discussion

A systematic activation of clotting system has been observed in cancer patients by subclinical abnormalities of conventional coagulation tests [14]. There are some evidences that the activation of coagulation system by neoplastic cells facilitates invasiveness and metastases [15]. Fibrinogen is one of the important parameters concerning the relationship between malignancy and coagulation disorders. In our study, the plasma fibrinogen level was significantly correlated with WBC and platelet counts. This is probably evidence that high plasma fibrinogen levels are indicative of, not only a coagulation factor but also an acute phase reactant protein that is greatly enhanced in response to infection and other inflammatory disorders. In addition, we also find that a higher plasma fibrinogen concentration was associated with squamous cell carcinoma versus adenocarcinoma; the result is similar with a current research, which indicated plasma fibrinogen level is associated with histological type [8].

Recent clinical researches have shown that plasma fibrinogen level is associated with the lymph nodes and distant organ metastases of malignant tumour [16-18]. However, the relationship between the plasma fibrinogen level and lung cancer stage still remains unclear. In our study, there is a significant association between plasma fibrinogen levels and cancer stage, pointing a higher plasma fibrinogen level in patients with advanced NSCLC (IIIB-IV). Furthermore, ROC analysis of plasma fibrinogen concentration indicates that plasma fibrinogen level can be a useful predictor for nodes or distant organ metastases. In conclusion, this study gains further evidence for prognostic value of the relationship between lung cancer stage and fibrinogen.

A link between hyperfibrinogenemia and malignant diseases has previously been revealed. It is increasingly recognized that the plasma fibrinogen levels have prognostic significance in several cancers [3−5]. The recent researches about lung cancer have shown that basal plasma fibrinogen levels could be used as an independent prognostic parameter for the OS of patients with advanced NSCLC [8, 12]. However, another research showed that although high plasma fibrinogen level was associated with decreased survival in patients with lung cancer, it did not reach statistically significant difference through the study of 110 patients' [10]. In our study, the pre-treatment plasma fibrinogen levels were associated with OS in lung cancer which indicated high plasma fibrinogen concentration unfavourably impacted survival in lung cancer patients. Furthermore, our results suggested that the pre-treatment plasma fibrinogen level was also associated with OS in early stage NSCLC (stage: I-IIIA). Multivariate analyses also showed that pre-treatment fibrinogen level is an independent prognostic factor.

Recent clinical studies have shown that fibrinogen may be used for evaluating response to chemotherapy [19−21]. However, the relationship between the change of the plasma fibrinogen level after short-term chemotherapy and overall survival in patients with lung cancer still remains unclear. A recent research has shown that the change of the plasma fibrinogen levels between pre and post-chemotherapy is not associated with OS in 98 advanced NSCLC (cut off value $\Delta f = 0$) [9]. The result is similar with our study. However, we find that the condition of the elevation by more than 15% in fibrinogen level after short-term chemotherapy is associated with shorter OS in 56 patients (cut off value $\Delta f = 15\%$), which indicates the potential value of the change of fibrinogen between pre and post-treatment for predicting the OS. What's more, we also found that the patients with a low pre-treatment plasma fibrinogen level would have a shorter OS if the fibrinogen levels increased significantly after short-term chemotherapy. Furthermore, we also found that the patients with a high pre-treatment plasma fibrinogen concentration would have a longer OS if the fibrinogen levels decreased significantly after short-term chemotherapy, which indicated the value of early anticoagulation treatment. As is known to all, fibrinogen is recognized by multiple integrin and non-integrin receptors found on tumor cells, stromal cells, and inflammatory cells. The cellular interactions of fibrinogen mediated by specific receptors may control cell proliferation, cell migration, apoptosis, and expression of inflammatory

mediators [22]. Furthermore, the proliferative characteristics of tumour cells and the interaction with different stromal cells and supportive tissue govern how the tumors grow. It has been found that most solid tumours contain a substantial amount of fibrinogen; this is frequently deposited around solid tumours, which suggested that fibrinogen may promote the formation of tumour stroma. Fibrinogen forms a coating on the surfaces of tumor cells, and serves as a scaffold to support the binding of growth factors and to promote tumour cell dispersion in a manner analogous to wound repair along with other adhesive glycoproteins. Simultaneously, the coating of fibrinogen could also protect tumour cells from immune surveillance and prolong malignant cell survival [23]. So we hypothesize that the change of the plasma fibrinogen level after receiving platinum based chemotherapy may predicate the prognosis of lung cancer patients by the response for chemotherapy of the tumor cell. The condition that the plasma fibrinogen levels increase significantly after short-term chemotherapy may indicate the bad chemotherapeutic response and the progressive disease. To the best of our knowledge, no study has focused on correlation between the change of the plasma fibrinogen level and OS. We hope that there will be more large scale studies for validation.

Conclusions

First, elevated pre-treatment plasma fibrinogen levels were associated with male gender. Furthermore, pre-treatment plasma fibrinogen levels were associated with WBC and platelets, histological type. Secondly, there was a significant association between plasma fibrinogen levels and lung cancer stage. Thirdly, high pre-treatment plasma fibrinogen levels were significantly associated with shorter OS in 370 patients with lung cancer. In addition, high pre-treatment plasma fibrinogen levels were associated with shorter OS in 194 patients with early stage lung cancer (stage: I-IIIA). Finally, we found that the significantly chemotherapy-induced change in the plasma fibrinogen level related to the prognosis through a small sample study of 56 patients. These findings highlight the potential benefit of a new therapeutic strategy. This will entail the future development of practical methods for the inhibition of fibrinogen that will be evaluated in large scale studies.

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Conflict of interest

The authors wish to express that they have no conflict of interest.

Appendix

Appendix associated with this article can be found at http://www.nobleresearch.org/Journals/JCRT/Volume1/ 2052-4994_2014-3.aspx.

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