Prognostic significance of plasma D-dimer levels in patients with lung cancer

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Abstract

***Background* – The peripheral blood concentrations of several proteases of the clotting system have been shown to predict survival in patients with malignancy. A study was undertaken to investigate the independent value of the plasma levels of the D-dimer degradation product of fibrin before treatment for predicting prognosis in patients with lung cancer.**

***Methods* – The study comprised 70 patients with lung cancer (49 non-small cell lung cancer and 21 small cell lung cancer). Plasma levels of D-dimer were measured using an enzyme immunoassay kit. Multivariate statistical analysis was carried out using the Cox's proportional hazards model.**

***Results* – The median value of the plasma level of D-dimer differentiated two groups of patients with different outcomes: a group with a D-dimer level of <150 ng/ml (low DD group) and those with D-dimer levels of ≥150 ng/ml (high DD group). Survival time was significantly better in patients in the low DD group than in those in the high DD group in all patients (hazard ratio for high DD group = 4.7; 95% confidence interval (CI) 1.8 to 11.7). The plasma levels of D-dimer predicted survival independently from the clinical stage of disease, histological type, performance status, and tumour size (hazard ratio = 3.9; 95% CI 1.6 to 9.2).**

***Conclusions* – These results suggest that plasma levels of D-dimer might be useful for predicting the clinical outcome in patients with lung cancer. However, further prospective studies are needed in a larger population to confirm these findings.**

(*Thorax* 1997;**52**:563–565)

Keywords: D-dimer, lung cancer, prognosis.

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Received 9 August 1996
Returned to authors 23 October 1996
Revised version received 13 February 1997
Accepted for publication 20 February 1997

Systemic activation of the clotting system occurs frequently in patients with lung cancer.[1] The biological significance of the haemostatic abnormalities in cancer is not clear. There is some evidence to suggest that the capacity of neoplastic cells to activate the coagulation system and to express increased fibrinolytic activity facilitates their growth and contributes to their invasive and metastatic behaviour.[2] Plasmin generation induced by tumour cells may influence their invasiveness and capacity to produce metastasis by its ability to degrade protein components of the extracellular matrix, activate latent enzymes such as type IV collagenase, and dissolve tumour associated fibrin clots.[2] Circulating markers of the fibrinolysis system are raised in patients with lung cancer and they have been shown to correlate with tumour burden, clinical progression, and the response to chemotherapy.[3] The aim of this study was to investigate the independent value of the pretreated plasma levels of D-dimer fibrin degradation products for predicting prognosis in patients with lung cancer.

Methods

Seventy consecutive patients with lung cancer, of median age 65 years (range 20–83), admitted to the Mie University Hospital from July 1990 to December 1991 took part in the study. There were 49 cases with non-small cell lung cancer (non-SCLC) and 21 with small cell lung cancer (SCLC). Clinical staging was performed according to the new international staging system. Patients underwent curative surgery (n = 20) or combination chemotherapy followed by radiotherapy (n = 50). Venous blood samples were taken 1–5 days (median two days) before starting any treatment and stored at −80°C until needed. Plasma levels of D-dimer were determined using an enzyme immunoassay kit (Dimertest, Agen, Mountain View, California, USA). D-dimer levels were also measured in blood samples from age matched healthy volunteers (n = 40) and from patients with benign pulmonary disease (n = 25). There was a history of smoking in 50 patients with lung cancer, in 15 with benign disease, and in 10 healthy subjects. The intra-assay and inter-assay precision of D-dimer concentrations was 5.4% and 9.5%, respectively. Written consent was obtained from all subjects and the investigation was carried out according to the conditions of the Helsinki declaration.

STATISTICAL ANALYSIS

Data are expressed as mean (SE) values. The Student's *t* test was used to compare means between groups where appropriate. A p value of <0.05 was considered to be statistically significant. Survival time was calculated from the date of diagnosis of the disease to the date of death from the disease. Patients lost to follow up and deaths from different causes were considered as censored observations. The independent prognostic value of D-dimer and that of other factors were analysed by Cox's proportional hazards model.[4] The cut off value

of D-dimer levels for distinguishing prognostic groups was taken as the median value calculated by the box-and-whisker plot.

Results

Patients were followed up for a total of six years (median 15 months; range 2–66 months); 27 were censored observations. The plasma level of D-dimer was significantly higher ($p<0.0001$) in patients with lung cancer (276.7 (34.2) ng/ml) than in healthy controls (52.8 (3.9) ng/ml) or in those with benign disease (81.1 (7.5) ng/ml). A significant correlation was found between plasma levels of D-dimer and survival time ($r=-0.6$; $p<0.0001$). The median plasma level of D-dimer differentiated between two groups of patients with different outcomes: a group with a D-dimer level of <150 ng/ml (low DD group) and another with a D-dimer level of ≥ 150 ng/ml (high DD group). Survival time was significantly longer in all cancer patients in the low DD group than in those in the high DD group (hazard ratio (HR) = 4.7; 95% confidence interval (CI) 1.8 to 11.7; $p<0.0005$; fig 1A). There was a significant difference in survival between patients with low and high plasma levels of D-dimer in those with non-SCLC (HR for high DD group = 4.6; 95% CI 1.8 to 11.6; $p<0.002$; fig 1B) but not in those with SCLC (data not shown). Prognosis was also better in the low DD group than in the high DD group in patients with non-SCLC with extensive disease (HR = 6.4; 95% CI 1.4 to 28.6; $p<0.02$; fig 1C). The numbers of patients with non-SCLC with limited disease and of SCLC cases were not sufficient to allow statistical evaluation. The plasma level of D-dimer as a binary variable (high or low) predicted survival in all patients independently from other prognostic factors (HR = 3.9; 95% CI 1.6 to 9.2; $p=0.001$) including clinical stage, performance status, and tumour size.

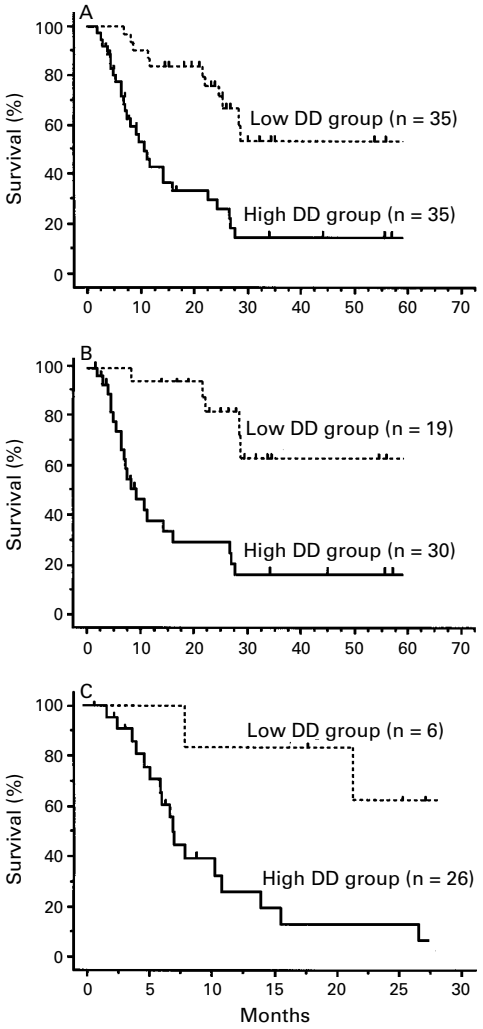

Figure 1 Effect of plasma levels of D-dimer (DD) on survival in (A) all patients with lung cancer, (B) all patients with non-small cell lung cancer (non-SCLC), and (C) all patients with non-SCLC with extensive disease. Vertical lines represent censored observations.

Discussion

Activation of fibrinolysis secondary to activation of coagulation is a well recognised complication in patients with lung cancer.[5] The biological significance of the activation of the clotting system and fibrinolysis in cancer has recently been discussed with regard to the potential role of these pathways in the pathogenesis of malignancy for their ability to regulate tumour growth and dissemination.[6] In this regard, anticoagulant therapy was reported to suppress the invasion of cancer cells in experimental models and to show survival benefit in some types of lung tumour in humans when used in combination with other cytotoxic drugs.[7] Fibrin deposits in lung cancer tissues may promote cell proliferation and neovascularisation of the growing tumour, and they may protect tumour cells from immune or chemotherapeutic attacks and favour their capillary implantation.[8] On the other hand, the fibrin framework in primary tumours may also block the entrance of tumour cells into the circulation.[8] However, lung cancer cells also express urokinase and tissue plasminogen activators which, by acting on plasminogen, generate plasmin – the active serine protease of the fibrinolysis system – that may act on fibrin in the primary tumours increasing the detachment of cells and their penetration into the circulatory channels.[9] In addition, plasmin may promote tumour invasion by degrading various protein components of the extracellular matrix, either directly or through the activation of various procollagenases such as procollagenase type IV secreted by tumour cells.[9] In this study the blood concentration of the fibrin degradation fragment D-dimer was found to be an independent predictor of survival in patients with lung cancer. The prognostic significance of this fibrinolytic marker may reflect the participation of plasmin in the process of tumour spread. In agreement with this, the plasma levels of protease components of the fibrinolysis system have also been found to be abnormally raised and to predict survival in lung cancer patients.[10] However, further prospective studies

must be carried out in a larger population to confirm our preliminary findings.

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Thorax 1997;**52**:565–568

Attenuation of oxidant/antioxidant imbalance during treatment of exacerbations of chronic obstructive pulmonary disease

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Abstract

***Background* – An oxidant/antioxidant imbalance is thought to occur in patients with chronic obstructive pulmonary disease (COPD). It has recently been shown that during exacerbations of COPD the antioxidant capacity and protein sulfhydryls of plasma are lower and the levels of products of lipid peroxidation are higher than in age matched healthy subjects. The aims of this study were to confirm these data and to measure the time course of these changes.**

***Methods* – The plasma Trolox equivalent antioxidant capacity (TEAC), protein sulfhydryls, and products of lipid peroxidation were measured throughout the course of treatment in 13 patients who presented with an acute exacerbation of COPD.**

***Results* – TEAC values (mmol/l) were low on admission (mean 0.67, 95% confidence interval (CI) 0.32 to 0.88; p<0.05) and had increased by discharge (0.98, 95% CI 0.88 to 1.2; p<0.05) but still remained lower than in healthy subjects (1.33, 95% CI 1.11 to 1.65). There was also restoration of plasma protein sulfhydryl levels (mmol/l) from admission (0.32, 95% CI 0.20 to 0.43) to discharge (0.49, 95% CI 0.42 to 0.62, p <0.001) to levels similar to those in healthy subjects (0.52, 95% CI 0.43 to 0.65). Products of lipid peroxidation, measured as thiobarbituric acid-malondialdehyde adducts (µmol/l), were significantly higher (2.08, 95% CI 1.8 to 2.5) than in control subjects (1.3, 95% CI 0.85 to 1.32; p<0.01) and returned to normal values by the time of discharge (1.2, 95% CI 0.88 to 1.29).**

***Conclusions* – These data confirm the presence of a profound oxidant/antioxidant imbalance in the blood of patients with acute exacerbations of COPD which returns towards normal values during the course of treatment.**

(*Thorax* 1997;**52**:565–568)

Keywords: oxidants, antioxidants, chronic obstructive pulmonary disease, lipid peroxides.

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Received 26 February 1997
Accepted for publication
27 February 1997

An oxidant/antioxidant imbalance is thought to play a part in the pathogenesis of chronic obstructive pulmonary disease (COPD).[1] Cigarette smoke and the release of reactive oxygen intermediates (ROI) from circulating neutrophils and airspace macrophages are major sources of oxidant stress in patients with COPD.[1]

There is, however, a paucity of data on the oxidant/antioxidant imbalance in patients with COPD, particularly during exacerbations. We have recently shown that the antioxidant capacity of plasma is lower during exacerbations of COPD than in age matched healthy subjects or patients with clinically stable COPD, suggesting increased oxidant stress.[2] This previous study was conducted in parallel groups of patients with either clinically stable or exacerbations of COPD. In the present study our aim was to assess the time course of the changes in markers of oxidant stress in plasma in individual patients during the course of an exacerbation of COPD.

Methods

STUDY POPULATION

Thirteen patients (six men) of mean (SD) age 69 (8) years who presented with an acute exacerbation of COPD were studied. The diagnosis of COPD was made by a respiratory