Pergamon

European Journal of Cancer Vol. 33, No. 1, pp. 50–55, 1997

Printed in Great Britain
0959-8049/97 $17.00+0.00

PII: S0959-8049(96)00310-3

Original Paper

Haemostatic Abnormalities in Lung Cancer: Prognostic Implications*

G. Buccheri,[1] D. Ferrigno,[1] C. Ginardi[2] and C. Zuliani[2]

[1]Pulmonary Departments of the "A. Carle" Hospital, I-12100 Cuneo; and [2]Laboratory of Clinical Pathology, "S. Croce" General Hospital, I-12100 Cuneo, Italy

Both experimental and clinical data have shown that coagulation disorders are common in patients with cancer although clinical symptoms occur rarely. A prethrombotic state is probably involved in the mechanism of metastatic spread. Anticoagulant treatment, with either warfarin or heparin, has been shown to have a positive influence in small cell lung cancer. The purpose of this study was to evaluate the prethrombotic state as a possible marker of the outcome of lung cancer. Pretreatment prothrombin time (PT), partial thromboplastin time (PTT), antithrombin III (AT-III), platelet blood count (P), fibrinogen (F) and D-dimer (DD) were prospectively recorded in a series of 286 consecutive patients with a new primary lung cancer. Other recorded variables (32 in all) consisted of a set of anthropometric, clinical, physical, laboratory, radiological and pathological data. All patients were carefully followed up, and their subsequent clinical course recorded. Spearman rank correlation tests between coagulation factors were weakly significant, or more often non-significant. The best correlation index was that between PT and PTT ($r_s = -0.25$). Univariate analyses of survival showed that a prolonged value of PT ($P = 0.00167$) and higher values of F ($P = 0.00143$) and DD ($P = 0.0005$) were associated with a poor prognosis. A few, weak relationships between well-known prognostic variables and coagulation abnormalities were also found. Because of the weakness of this correlation pattern, coagulation factors emerged in all the Cox's regression analyses as important predictors of survival, regardless of the number and type of cofactors used. A prethrombotic state (depicted by a prolongation of PT and increase of DD) is confirmed in this study as an aggravating condition in lung cancer. Studies attempting to reverse possible haemostatic abnormalities with the use of anticoagulants are justified by the present data.

Key words: lung cancer, prognosis, blood coagulation, prethrombotic state

Eur J Cancer, Vol. 33, No. 1, pp. 50–55, 1997

INTRODUCTION

AN INCREASED risk of thromboembolic episodes may occur in cancer. In 1865, in a treatise on the propensity of cancer patients to develop thrombophlebitis complications, Professor Armand Trousseau for the first time drew attention to the link between cancer and 'hyper-coagulability'. He wrote: 'There appears in the cachexia...a particular condition of the blood that predisposes it to spontaneous coagulation' [1]. A few years later, in a classic paper by Billroth [2], the relationship between cancer and thrombosis was reaffirmed. Today, the suggestions by Trousseau and Billroth are strengthened by new evidence. Studies of both routine [3] and specialised [4–8] tests of blood coagulation are many, and include patients with lung cancer. All have confirmed the existence of an association between some haemostatic abnormalities and cancer [3–8].

Clinical and experimental data also suggest that the activation of the coagulation system may promote the mechanism of metastasis formation [9–11]. Thzais may result in increased cancer aggressiveness, and shortened patient survival. The reversal of possible thromboembolic states with

*This paper has been presented in part at the 1995 European Conference of Clinical Oncology (ECCO 8), held in Paris, France, 29 October–2 November.

Correspondence to G. Buccheri.

Received 31 Jan. 1996; revised 27 Jun. 1996; accepted 9 Aug. 1996.

anticoagulant treatments has positively influenced the prognosis of some cancer patients [12–14]. The aims of this study were to determine whether some coagulation abnormalities are more frequently associated with lung cancer; to explore the possible correlation between such abnormalities and other clinical and laboratory characteristics; and to evaluate whether the presence of a prethrombotic state may function as a marker of disease. In particular, we were interested to see whether clotting abnormalities were capable of predicting the patients' outcome independently of other well-known prognostic clinical indicators.

We evaluated the subclinical activation of the coagulation-fibrinolytic system, by measuring both routine clotting tests and a newly developed molecular marker of fibrinolysis, the cross-linked fibrin degradation fragments D-dimer (DD).

PATIENTS AND METHODS

Patients

All patients referred to the 'A. Carle' Hospital of Chest Diseases for a suspected bronchial tumour from July 1991 to August 1994 were considered. Eligibility criteria were a diagnosis of lung cancer confirmed by cytological specimens or biopsies and a relatively extensive diagnostic examination. This included clinical history and physical examination, determination of weight loss and both the Eastern Cooperative Oncology Group (ECOG) [15] and the Karnofsky [16] performance status assessments. A battery of laboratory tests, such as blood cell counts, serum chemistry, coagulation tests, and the measurement of the serum protein content [17] was routinely requested. The instrumental evaluation consisted of bronchoscopy, chest X-rays and tomograms, computed tomography of the thorax, brain and upper abdomen. Bone scans and bone marrow biopsies were obtained in most patients with small cell lung cancer. A total body indium-111 anticarcinoembryonic monoclonal antibody scintigraphy was performed in all consenting surgical candidates [18, 19]. Patients with dubious metastatic involvement were further investigated with appropriate imaging studies, biopsies or needle aspirations. In potentially resectable tumours, any radiological finding equivocal for nodal mediastinal involvement was considered an indication to mediastinoscopy. Cell type and tumour stages were classified according to internationally adopted criteria [20, 21].

Study design

The design of the study was prospective. We recorded 38 variables for each patient entered on study, including the following six coagulation factors: platelet count (P), prothrombin time (PT), partial thromboplastin time (PTT), antithrombin III (AT-III), fibrinogen (F) and DD. The other recorded variables were age, sex, Karnofsky and ECOG performance status, weight loss, haemoglobin blood content, total white cell/neutrophil counts, erythrocyte sedimentation rate, tumour cell type, clinical stage, and the T, N, and M factor. In addition, we measured and recorded the serum concentration of each of the following enzymes and substances: lactate dehydrogenase, alkaline phosphatase, pyruvic and oxalacetic transaminases, creatine, uric acid, sodium, total protein, immunoglobulin A, G and M, transferrin, alpha 1-antitrypsin, haptoglobin, alpha-1-glycoprotein, alpha-2-macroglobin, carcinoembryonic antigen and tissue polypeptide antigen.

Follow-up programmes consisted of clinical, laboratory and radiological reassessments performed at 3–4 week intervals during chemotherapy, and every 3–6 weeks in case of palliative radiotherapy, or no anticancer treatment. Patients treated with radical surgery were scheduled to be visited at longer intervals, ranging 3–6 months. Very few patients abandoned their follow-up programme; in such cases, the status (alive or dead) was learned by a telephone interview with the patient, the family, the house doctor, or the municipal office of the registry.

Consequently, both the duration of survival, measured from the first hospital admission or outpatient visit, and the status of dead or alive at the closure of the study (i.e. at December 1994) was available for all patients.

Coagulation assays

PT, PTT, AT-III and F were measured using commercially available reagents provided by the Ortho Diagnostic System Inc. (Johnson & Johnson Co., New Jersey, U.S.A.) following the manufacturer's instructions. The blood concentration of fibrin degradation products, D-dimers, was measured by a monoclonal antibody and a latex agglutination test, using the D-dimer test kit supplied by the Boehringer Mannheim Co. (Mannheim, Germany). The blood samples of patients were drawn before initiation of therapy and processed immediately, except for AT-III measurements. Blood samples for this latter test were stored at -20° until analysed.

Statistical analysis

Non-parametric tests [22] were used to assess statistically relationships and differences among coagulation factors or between these factors and the other variables placed on record (i.e. Spearman rank, Kruskall–Wallis and median test, as appropriate).

Univariate analyses of survival were accomplished categorising continuous variables in values lower or equal to the median and values above the median. They were based on the Kaplan–Meier product-limit estimates of the distribution [23]. Differences between actuarial curves were tested using the Mantx–Cox log rank test, offered by the STATISTICA software. The relative importance of multiple prognostic factors on survival was estimated using the Cox's proportional hazards regression model [24]. For survival analyses, a P value of less than 0.05 was set as significant. All tests were two sided. The STATISTICA package (statsoft, Inc., Tulsa, Oklahoma, U.S.A.) was used for data processing.

RESULTS

From July 1991 to August 1994, 286 consecutive patients were entered into the study. Of these, 32 abandoned their follow-up programme; none were lost to the follow-up. Descriptive characteristics of the study population are shown in Table 1.

Coagulation factors and their correlation with other clinical and laboratory variables

Table 1 reports the number of observations, and either the frequency distribution or the median and range for all

Table 1. Descriptive characteristics of the cohort studied and the variables recorded

Characteristic	Observations	Median (range) or frequency
Age (years)	286	61 (32–87)
Sex (M/F)	286	255/31
Karnofsky performance status	285	80 (40–100)
ECOG performance status	285	2 (0–4)
Weight loss (weight in % of prior 6 months)	283	95 (74–110)
Haemoglobin (g/dl)	283	13.9 (8.0–1.20)
White blood cells (no./mm^3)	283	8740 (4000–25 530)
Neutrophils (no./mm^3)	279	5860 (1970–22 220)
Platelets (no./mm^3)	280	296 (149–982)
Lactate dehydrogenase (mg/dl)	275	319 (126–2989)
Alkaline phosphatase (mg/dl)	280	134 (19–536)
Glutamic pyruvic transaminase (mg/dl)	282	18 (5–161)
Glutamic oxalacetic transaminase (mg/dl)	282	17 (2–259)
Uric acid (mg/dl)	272	5.1 (1.6–13.6)
Creatine (mg/dl)	282	1 (0.5–10.9)
Sodium (mEq/ml)	280	140 (119–148)
Erythrocyte sedimentation rate	274	34 (2–120)
Total protein content (g/dl)	278	7 (4.6–9.1)
Immunoglobulin A (mg/dl)	270	326 (118–951)
Immunoglobulin G (mg/dl)	270	1350 (590–2700)
Immunoglobulin M (mg/dl)	270	110 (30–540)
Transferrin (mg/ml)	268	220 (120–480)
Alpha-1-antitrypsin (mg/dl)	265	282 (155–669)
Haptoglobin (mg/dl)	267	385 (85– 960)
Alpha-1-acid glycoprotein (mg/dl)	268	133 (52–389)
Alpha-2-macroglobin (mg/dl)	267	196 (125–549)
Carcinoembryonic antigen (mg/dl)	271	2 (0–790)
Tissue polypeptide antigen (U/L)	268	140 (20–4000)
Prothrombin time (%)	276	97 (37–160)
Partial thromboplastin time (sec)	273	29 (2–48)
Antithrombin III (%)	233	94 (26–128)
Fibrinogen (mg/dl)	247	429 (142–940)
D-dimer (μg/ml)	234	0.5 (0–4)
Histology (E/S/A/L/U)*	286	112/37/67/18/52
Stage of disease (1/2/3a/3b/4)	286	42/31/119/94
T factor (0/1/2/3/4)	286	41/105/44/96
N factor (0/1/2/3)	286	98/34/96/58
M factor (0/1)	286	192/94

E, epidermoid carcinomas; S, small cell lung cancers; A, adenocarcinomas; L, large cell anaplastic carcinomas; U, mixed histology or unclassified carcinomas.

38 variables considered, including the six coagulation tests. 49 patients (19%) had manifest thrombocytosis ($\geqslant$ 400000/mm^3), 12 (4%) were thrombocytopenic. PT was below 75% in 21 cases (8%). 23 patients (8%) had frankly reduced times of PTT 9 < 26 sec.). F, AT-III and DD were abnormal in 145 (59%), 41 (18%) and 144 patients (62%), respectively. In particular, increased values of F and DD were obtained in 143 and 144 cases, while AT-III was abnormally reduced in 36 subjects.

No coagulation factor showed increased abnormalities according to the cell type (P values of the differences were between 0.48 and 0.08, Kruskall–Wallis test). Gender was also non-influential. Multiple correlation tests among the 38 variables revealed only weakly significant or non-significant associations between coagulation factors, the strongest being that between PT and PTT (Spearman r [r_S] = 0.25). Analogously, relationships between coagulation and non-coagulation factors were rarely significant. The most significant associations were those between platelet and white blood cell/neutrophil counts (r_S = 0.37/0.38), haemoglobin (r_S = – 0.32), alkaline phosphatase (r_S = 0.31) and creatinine (r_S = – 0.29). Other significant relationships were AT-III and haemoglobin (r_S = 0.22), F and weight loss (r_S = – 0.21), F and alkaline phosphatase (r_S = 0.46), F and the tissue polypeptide antigen (r_S = 0.29), F and creatinine/uric acid (r_S = – 0.25/ – 0.21), F and HB (r_S = – 0.29), F and white cell/neutrophil counts (r_S = – 0.24/0.33), DD and Karnofsky performance status (r_S = – 0.27), and, finally, DD and lactate dehydrogenase (r_S = 0.20).

Survival analysis

Univariate analyses of survival revealed that P, PTT and AT-III were unrelated to the patients' outcome (P = 0.249 for the platelet count, 0.164 for the partial thromboplastin time, and 0.326 for the anti-thrombin III). On the contrary, values below the median of PT (Figure 1a) and F (Figure 1b), or abnormally elevated concentrations of DD (Figure 1c) were strongly predictive of a poor prognosis.

Multivariate analyses of survival were accomplished with no prior dichotomisation or categorisation of the continuous variables. We performed three types of multivariate analysis.

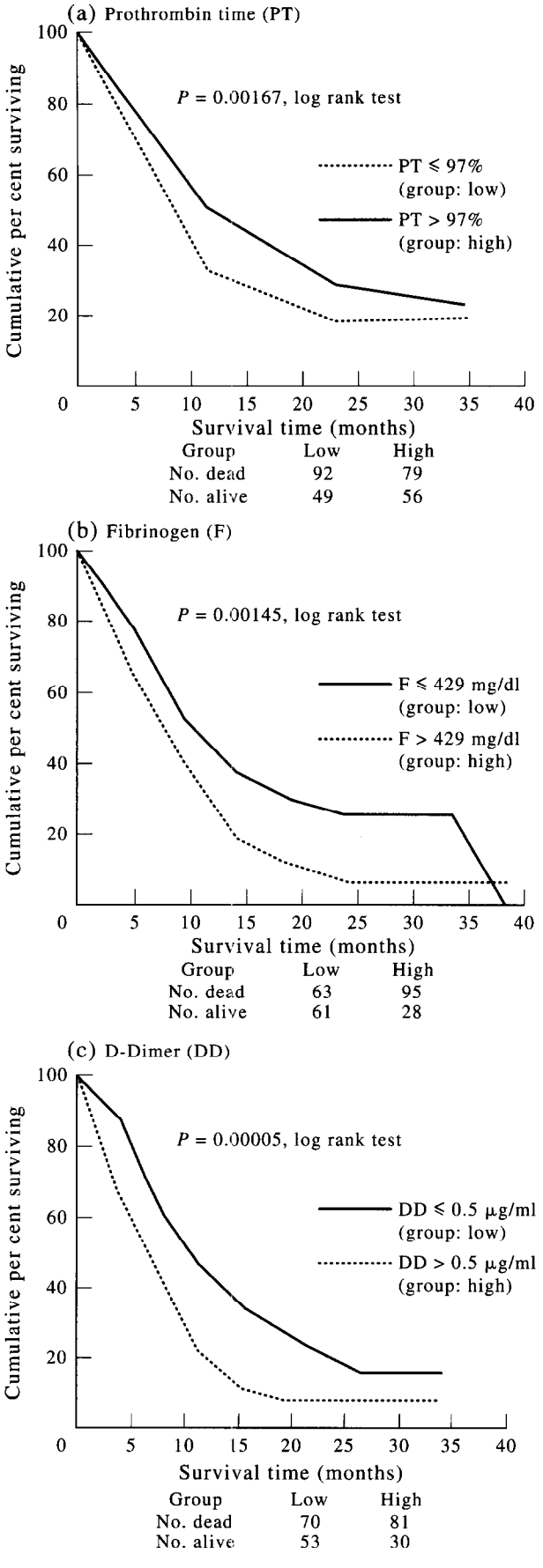

Figure 1. Survival probability based on the result of the (a) prothrombin time; (b) fibrinogen test; (c) D-dimer test.

In the first proportional hazards regression analysis (Table 2), we considered all 38 recorded variables. In the resulting model, significant determinants of survival were, in order of descending importance, N factor, PT, erythrocyte sedimentation rate, lactate dehydrogenase, ECOG performance status, platelet blood count, and alpha-1-glycoprotein. Importantly, two coagulation factors, along with other laboratory parameters, replaced other powerful prognostic indicators, such as the stage of disease or the presence of a metastasis.

Reducing the number of variables may be useful to increase the number of valid observations and thus the statistical power of a test, provided, of course, that essential information is not then lost. We did a second Cox's analysis including only sex, weight loss, ECOG performance status, cell type and clinical stage in addition to the six coagulation parameters (valid cases = 218, $\chi^2 = 83.8$, df = 11, $P = 0.00000$). In this analysis, prothrombin time was a very important factor, following clinical stage and preceding ECOG performance status within the group of explanatory variables for the model.

A multivariate model limited to the clotting factors may corroborate the results of the univariate analyses and help to establish a ranking scale among those that are prognostically important. A third regression analysis based on the six clotting variables only (valid cases = 222, $\chi^2 = 29.14$, df = 6, $P = 0.00006$) confirmed the significance of factors significant in univariate analysis. The following order of clinical relevance was obtained: (1) D-dimer; (2) PT; and (3) F.

DISCUSSION

Abnormalities of the clotting-fibrinolytic system are well-known companions of cancer [25]. Although thromboembolic disorders of clinical significance and diffuse intravascular coagulation have been reported to occur in only a small fraction of patients with cancer, subclinical abnormalities of conventional tests of blood coagulation have been reported occasionally [25]. Their relative frequency was examined in a large, prospective, multi-institutional Veterans Administration cooperative study [3]. The most common abnormalities observed in a sample of more than 1000 patients with head and neck cancer, lung cancer, colon cancer, or prostate cancers were thrombocytosis (45%) and hyperfibrinogenaemia (51%) [3].

The current study confirms that subclinical changes in the coagulation-fibrinolytic system are often present in lung cancer. We considered five conventional and one new test of blood coagulation (i.e. P, PT, PTT, F, AT-III, DD), detecting significant departures from the expected values for any of the above tests. Reactive thrombocytosis results from accelerated platelet production, although the stimulus for such overproduction is unknown. It occurs in response to haemorrhage, haemolysis, infections, inflammatory disorders and carcinomas [26]. In our series of patients with pulmonary cancer, we found an elevation of the platelet count above $400/m^3$ in 49 of 280 assessable cases (18%). Hyperfibrinogenaemia is found in the same clinical states that usually accompany thrombocytosis [26]. Fibrinogen is an acute phase reactant, whose blood concentration may increase in concomitance with the elevation of the other serum proteins. An elevation of acute phase reaction proteins is frequently observed in lung cancer and has clinical

*Table 2. Statistically significant factors in the Cox's multivariate regression model including all the 38 variables described in Table 1**

Variable	Beta	Standard error	t-value	*P*-value
N factor	0.45	0.13	3.54	0.0011
Prothrombin time	−0.04	0.01	−3.24	0.0025
Erythrocyte sedimentation rate	−0.02	0.01	−2.70	0.0103
Lactate dehydrogenase	0.01	0.01	2.51	0.0165
ECOG performance status	0.48	0.20	2.39	0.0219
Platelets	−0.01	0.01	−2.10	0.0424
Alpha-1-glycoprotein	0.01	0.01	2.04	0.0483

*146 cases included; global $\chi^2 = 119.055$; global $P = 0.00000$.

momentum [17]. In this study, hyperfibrinogenaemia was particularly common (it was present in 58% of the patients). The prothrombin time is a screening test for plasma deficiencies in the extrinsic system (factor VII), and for deficiencies of factors common to the extrinsic and intrinsic systems, such as factor X, factor V, prothrombin and fibrinogen [26]. In our patients, we observed a significant reduction of PT in 33 cases (12% of the sample). The partial thromboplastin time, assuming a normal fibrinogen level, screens for deficiencies of factors in the intrinsic system (XII, XI, IX, VIII) or deficiencies of factors common to the intrinsic and extrinsic system [26]. In our study, only 2 of 273 patients had abnormally prolonged PTT. Among the plasma proteins that serve as potent inhibitors of blood coagulation, antithrombin-III is a particularly effective inhibitor of activated factor X and thrombin, but it also blocks the activity of other blood blotting proteases [26]. Of our patients, 36% showed a reduced AT-III. Although insensitive, PT, PTT and AT-III may be reduced as an effect of a disseminated intravascular coagulation [27, 28]. In the subclinical phase, platelet count and fibrinogen may be normal, or even increased because of overcompensation or in response to some stimuli, such as infections or inflammation [27, 28]. Among the newly isolated markers used to evaluate several aspects of the clotting-fibrinolytic system, the cross-linked fibrin-derived product, DD, results from the proteolytic actions of plasmin on fibrin [28]. It is considered a sensitive marker of fibrinolytic enhancement [28]. We found that most patients with lung neoplasia had an increased plasma level of DD.

Another point of interest is based on the many clinical correlates attempted between coagulation factors and anthropometric, historical, physical, laboratory, radiological, pathological and outcome variables, recorded for each patient at the time of the initial diagnosis. In this context, we observed a few prognostically important relationships. In fact, clotting parameters did not correlate, or correlated almost exclusively with variables having weak or dubious prognostic value. For example, the most statistically significant correlation was that of platelets with either white blood cell and neutrophil counts, or haemoglobin, alkaline phosphatase and creatinine. Other prognostically non-significant associations were those between AT-III and haemoglobin, F and alkaline phosphatase, F and creatine/uric acid, F and white cell/neutropohil counts, F and haemoglobin. Only F (weight loss and tissue polypeptide antigen), and DD (Karnofsky performance status and lactate dehydrogenase) correlated with two well-established prognostic determinants [29].

The core of this study, however, is founded on the several survival analyses exploring the possible prognostic significance of blood coagulation. We were able to show that several clotting tests were strongly predictive of the prognosis, in both univariate and multivariate models. Univariate tests showed that lower values of PT, higher values of F, and abnormally elevated concentrations of DD were all significantly associated with an adverse outcome. Lower values of PTT were also associated with shorter survivals, but this relationship did not reach significance ($P = 0.1$). The multivariate models confirmed that several clotting tests were predictors of survival independently of a quite large list of clinical prognosticators.

A subclinical activation of the clotting-fibrinolysis system, depicted by a prolongation of PT and PTT and an increase of DD [27] might have been the real cause of the enhanced risk of death in our cancer patients. This hypothesis is made stronger by the positive influence of anticoagulant treatments on the prognosis of several cancers [12–14], even though, at least theoretically, haemostatic alterations might be just an 'epiphenomenon' accompanying the real, unknown cause of the adverse outcome. Obviously, new clinical studies, attempting to reverse the possible presence of haematostatic abnormalities, are encouraged by the current findings.

In a recent article reviewing the prognostic factors for lung cancer [29], we considered a hundred of the potentially useful tests that may help in the assessment of lung cancer patients. We concluded that 'the myriad of the known and unknown prognostic factors of lung cancer recall a universe of constellations already known and constellations yet to be discovered...'. Clotting abnormalities may represent a new 'constellation' of effective prognostic factors. We hope that this study will stimulate other investigators to repeat and eventually confirm out present findings.

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Acknowledgement—The authors are indebted to the Cuneo Lung Cancer Study Group (Cu.L.Ca.S.G.) for technical and financial support.