Acta Oncologica 29 (1990) Fasc. 2

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BLOOD ANALYSES AS PROGNOSTIC FACTORS IN PRIMARY LUNG CANCER

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Abstract

The prognostic value of some pretreatment blood tests was analysed in a follow-up study of 189 patients with non-small cell lung cancer diagnosed in West-Norway between 1976 and 1985. At diagnosis 100 patients had stage III/IV disease. Five-year survival calculated with the life-table method was 12%. In univariate survival analyses significant prognostic factors were stage III/IV disease, weight loss, elevated lactate dehydrogenase, gamma glutamyl transferase, erythrocyte sedimentation rate and alkaline phosphatase, thrombocytosis, leukocytosis and anaemia. In multivariate survival analyses with the Cox's regression model stage III/IV disease, elevated lactate dehydrogenase, thrombocytes and erythrocyte sedimentation rate were significant prognostic factors. It is concluded that these blood analyses at diagnosis in non-small cell lung cancer patients may give additional prognostic information. The need for multivariate analyses is also demonstrated.

Key words: Non-small cell lung cancer, blood tests, prognostic factors.

Knowledge of prognostic factors is necessary both in planning and comparing cancer treatment regimens. In primary lung cancer initial performance status, extent of disease and weight loss are well-known prognostic factors for survival (1, 2). We have studied the prognostic value of some common pretreatment laboratory tests using a Cox's regression model.

Material and Methods

This follow-up study includes 189 patients (153 males and 36 females) with primary non-small cell lung cancer (NSCLC). Diagnosis was made at the lung department of the County Hospital in Molde between 1976 and 1985. The department serves a county in West-Norway with about 235000 inhabitants. The majority of lung cancer patients from this county is referred to the department. Histological diagnosis was made at the department of pathology and later reviewed in all patients. A total of 254 patients with primary bronchial cancer were diagnosed during the 10-year period. Diagnostic investigation included chest radiography (all patients), bronchoscopy with biopsies and brushing (except for 31 patients), cytological examination of sputum and when existing, of pleural fluid. When necessary transthoracic needle biopsies were performed. Twenty-five patients with uncertain histology and 40 patients with small cell lung cancer (SCLC) were excluded. Tumor classification was based on cytological specimens alone in 39 of the 189 patients. The distribution of patients by major histological groups is shown in Table 1.

Investigations for evaluating resectability included liver, bone and brain radionuclide scanning and abdominal ultrasonography. In addition, pulmonal angiography was performed in 37 patients, and scalene node biopsy in 53 patients. Since CT-scanner was not available except for the last year in this period, only 17 patients were referred for this investigation. Four patients had an explorative thoracotomy. In 20 patients, too ill or otherwise clearly inoperable, none of these special investigations were done. Extent of disease at time of diagnosis was recorded from preoperative data. Retrospectively, 100 patients had stage III or IV disease according to the TNM staging system (3). Eighteen of these had distant metastases (liver, bone, brain and/or other lung), and another 13 had supraclavicular lymph node metastases.

Only pretreatment blood samples attained before these procedures were recorded to avoid possible influence of invasive procedures on the blood parameters tested. All blood tests were analysed at the hospital's clinical chemical laboratory. Erythrocyte sedimentation rate (ESR) was

Accepted for publication 29 March 1989.

Table 1

Distribution of 189 non-small cell lung cancer patients by histological subgroups

WHO	I	Squamous cell carcinoma	112
WHO	III	Adenocarcinoma, including 10 with bronchio-alveolar cell type	67
WHO	IV	Large cell carcinoma	10

performed with the Westergren method. Sixteen patients had concomitant disease which might have influenced the ESR; eleven of these had symptoms of infection and five had rheumatic disease. Pretreatment laboratory variables are seen in Table 2 for all patients.

Weight loss was defined as 10% or more loss of body weight in 6 months.

Table 3 describes the various modes of treatment given to the patients. Forty-one patients were considered radically operated. Radiation therapy was given to 66 patients and chemotherapy to 51 patients.

Survival defined from time of diagnosis was calculated with the life-table method (4). Differences between survival curves were tested by the log-rank test (5). Cox's proportional hazards model (6) was used to simultaneously analyse the importance of several prognostic factors. By the end of the 10-year period 27 patients were alive. No patients were lost to follow-up during observation period. The cause of death in 8 patients was not regarded to be a result of the lung cancer. Their times of death were treated as censored observations (at risk until death). The proportional assumptions in the Cox's model were tested with plot, and continuous variables were grouped with cutpoints at quartiles. Neither laboratory variables nor age could be used in the continuous form without neglecting the proportional assumption. These variables were divided into two groups with a cutpoint near the quartile giving the best plot of proportional hazards. All variables were first tested individually with cutpoints as derived from the plots. Only significant variables from the univariate analyses were included in the multivariate survival analyses.

Results

The survival rates for all 189 patients after 2, 5 and 10 years were 27, 13 and 5% respectively. In Table 4 the results of the univariate survival analyses are shown. Multivariate survival analysis was first run for blood analyses only. Thrombocytes, lactate dehydrogenase (LDH) and ESR were the only significant variables.

When including all variables, the regression analyses selected stage III/IV disease, elevated LDH, thrombocytes and ESR as unfavourable prognostic factors (Table 5). The 16 patients with concomitant infectious or rheumatic disease were included in these analyses. To see if this could have influenced the results, the same analyses were done with these patients excluded. However, the same unfavourable prognostic factors were selected. In multivariate analyses cases with missing values are automatically excluded from the computer programme. Miss-

Table 2

Some pretreatment variables in 189 non-small cell lung cancer patients

Variable	n	Median	Range
Age, years	189	66	38–87
Hemoglobin, g/dl	189	13.4	8.7–17.6
Erythrocyte sedimentation rate, mm/h	189	32	1–140
Leukocytes $\times 10^9$/l	188	8.4	2.0–28.9
Thrombocytes $\times 10^9$/l	151	298	76–740
Lactate dehydrogenase, U/l	166	336	175–1 072
Gamma glutamyl transferase, U/l	161	20	8–493
Alkaline phosphatase, U/l	181	196	54–2 093

Table 3

Treatment in 189 non-small cell lung cancer patients

	n
Surgery	50
Irradiation	28
Irradiation and chemotherapy	24
Chemotherapy	14
Surgery, and later irradiation	7
Surgery, and later irradiation and chemotherapy	7
Surgery, and later chemotherapy	6
None of these	53

Table 4

Results of univariate survival analyses in 189 non-small cell lung cancer patients

Variable	n/total	Log-rank test p-values
Stage III–IV disease	100/189	<0.0001
Weight loss present	69/174	<0.0001
Gamma glutamyl transferase >40 U/l	37/161	<0.0001
Thrombocytes >300 $\times 10^9$/l	74/151	<0.0001
Lactate dehydrogenase >400 U/l	44/166	0.0001
Erythrocyte sedimentation rate >30 mm/h	96/189	0.0001
Leukocytes >10$\times 10^9$/l	60/188	<0.001
Alkaline phosphatase >250 U/l	38/181	0.001
Hemoglobin <12 g/dl	38/189	0.01

Sex, age, histological types, localization within the lungs, radiotherapy and chemotherapy were not significant variables.

Table 5

Multivariate survival analyses of preoperative data in 137 non-small cell lung cancer patients

Variable	Regression coefficient	Standard error	p-values
Stage III/IV disease vs others	0.80	0.21	<0.001
Lactate dehydrogenase >400 U/l vs others	0.78	0.22	<0.001
Thrombocytes >300×10^9/l vs others	0.63	0.21	<0.001
Erythrocyte sedimentation rate >30 mm/h vs others	0.58	0.22	<0.01

ing values, especially for thrombocyte count, in addition to those missing from other variables reduced the number of patients in Table 5 from 189 to 137. A multivariate analysis performed without including thrombocyte count (151 patients) selected weight loss, stage III/IV disease, elevated LDH, ESR and leukocyte count as significant variables.

Discussion

In multivariate survival analyses elevated LDH, thrombocyte count and ESR indicated, in addition to stage III/IV disease, high risk patients. Evaluation of disease extent for staging might have been more intensive in some of the patients, and in that case it might possibly have influenced the results of these analyses. With increasing costs in health services the possible use of cheap blood analyses in risk evaluation deserves attention.

Elevated levels of LDH have been reported to predict short survival in SCLC (7, 8). This was also found in a lung cancer material of mixed histopathology (9). There are few reports concerning LDH and NSCLC. Gail et al. (10) found an insignificant trend of increased death rates in resected NSCLC patients, stage I with elevated LDH, supported by our results. In several other types of cancer there are reports on LDH as a prognostic factor of survival, as in malignant lymphoma (11, 12), leukaemia (13), testicular neoplasms (14), neuroblastoma (15) and Ewing's sarcoma (16).

Thrombocytosis is a well-known phenomenon in lung cancer. Higher thrombocyte counts have been found in patients with extensive disease (17, 18) and in patients with shorter survival (19). To our knowledge this is the first report of preoperative thrombocytosis as a prognostic factor in NSCLC determined by the Cox's regression model. This study demonstrates the need for multivariate analyses. Nine variables were significant in the univariate analyses, but only four were selected in a final model by the regression analyses.

Elevated ESR, leukocytosis and thrombocytosis have been found associated with shorter survival in lung cancer (19). However, a multiple regression model was used in that study, and it was concluded that the predicting capacity of these three variables was rather low. If thrombocyte count was not tested as a possible predictor in our multivariate analyses due to many missing values, leukocytosis became a significant prognostic factor instead. Leukocytosis has been found associated with shorter survival in unresectable lung cancer (20). Both leukocytosis and thrombocytosis may be inflammatory responses to tissue damage caused by the cancer, or perhaps an effect of direct involvement of the bone marrow (21, 22). However, the correlation between leukocyte and thrombocyte count was small (correlation coefficient 0.16).

ESR was reported as an important prognostic factor in renal cell cancer already in 1970 (23). This has been confirmed in later studies of renal cell cancer, including one study based on multivariate analyses (24). Nevertheless, ESR is usually not tested at all in prognostic studies, and only a few other reports are found for gastric carcinoma (25), chronic lymphocytic leukaemia (26), breast cancer (27), colorectal cancer (28) and Hodgkin's disease (29).

Performance status was not available in this retrospective analysis. Other authors have found laboratory parameters as a good alternative to performance status (8). Weight loss is known as an important prognostic factor in lung cancer (1, 2). It was a strong prognostic factor in the univariate analyses in our study, but it was more frequently recorded in patients with stage III/IV disease and/or elevated thrombocyte count. In the stepwise regression analyses metastatic disease and/or elevated thrombocyte count were selected before weight loss. Then weight loss did not contribute further to predict survival in NSCLC.

ACKNOWLEDGEMENT

The authors acknowledge Dr Erik Engebjerg, Department of Pathology, Molde Hospital, for reviewing histological specimens.

Request for reprints: Dr Terje Engan, Department of Oncology, Regionsykehuset, N-7006 Trondheim, Norway.

REFERENCES

1. Stanley KE. Prognostic factors for survival in patients with inoperable lung cancer. JNCI 1980; 65: 25–33.
2. Lagakos SW. Prognostic factors for survival time in inoperable lung cancer. In: Straus M, ed. Lung cancer clinical diagnosis and treatment. New York: Grune & Stratton 1977: 271–80.
3. Mountain CF. A new international staging system for lung cancer. Chest 1986; 89: 225–33.
4. Cuthler S, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chron Dis 1958; 8: 699–712.
5. Peto R, Pike C, Armitage P, et al. Design and analysis of clinical trials requiring prolonged observation of each patient. Br J Cancer 1977; 35: 1–39.

6. Cox DR. Regression models and lifetables. J R Stat Soc 1972; 34: 187–220.
7. Østerlind K, Andersen PK. Prognostic factors in small cell lung cancer: Multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Res 1986; 46: 4189–94.
8. Cohen MH, Makuch R, Johnston-Early A, et al. Laboratory parameters as an alternative to performance status in prognostic stratification of patients with small cell lung cancer. Cancer Treat Rep 1981; 65: 187–95.
9. Buccheri GF, Violante B, Sartoris AM, Ferrigno D, Curcio A, Vola F. Clinical value of a multiple biomarker assay in patients with bronchogenic carcinoma. Cancer 1986; 57: 2389–96.
10. Gail MH, Eagan RT, Feld R, et al. Prognostic factors in patients with resected stage I non-small cell lung cancer. Cancer 1984; 54: 1802–13.
11. Ridgway D, Smiley S, Neerhout RC. The prognostic value of presenting serum LDH in non-Hodgkin lymphoma. J Pediatr 1981; 99: 611–3.
12. Schilling RF, McKnight B, Crowley JJ. Prognostic value of serum lactic dehydrogenase level in Hodgkin's disease. J Lab Clin Med 1982; 99: 382–7.
13. Gomez GA, Sokal JE, Walsh D. Prognostic features at diagnosis of chronic myelocytic leukemia. Cancer 1981; 47: 2470–7.
14. Lippert MC, Javadpour N. Lactic dehydrogenase in the monitoring and prognosis of testicular cancer. Cancer 1981; 48: 2274–8.
15. Quinn JJ, Altman AJ, Frantz CN. Serum lactic dehydrogenase, an indicator of tumor activity in neuroblastoma. J Pediatr 1980; 97: 89–91.
16. Brereton HD, Simon R, Pomeroy TC. Pretreatment serum lactate dehydrogenase predicting metastatic spread in Ewing's sarcoma. Ann Intern Med 1975; 83: 352–4.
17. Silvis SE, Turkbas N, Doscherholmen A. Thrombocytosis in patients with lung cancer. JAMA 1979; 211: 1852–3.
18. Diehl WL, Mandelbaum I. The significance of thrombocytosis in patients with carcinoma of the lung. Surg Gynecol Obstet 1983; 156: 187–8.
19. Gislason T, Nou E. Sedimentation rate, leucocytes, platelet count and haemoglobin in bronchial carcinoma: an epidemiological study. Eur J Respir Dis 1985; 66: 141–6.
20. Check IJ, Demeester T, Vardiman J, Hunter RL. Differential counts and survival in lung cancer. Lancet 1978; 2: 317–8.
21. Finch SC. Granulocytosis. In: Hematology. Williams WJ, Beutler E, Erslev AJ, Rundles R, eds. New York: McGraw-Hill Book Company 1977: 746–55.
22. Henson PM, Gordon JL. Cellular components of inflammation: platelets. In: Kelley WN, Harris ED, Ruddy S, Sledge CB, eds. Scientific bases of rheumatology. Philadelphia: Saunders 1985: 169–82.
23. Böttiger LE. Prognosis in renal cell carcinoma. Cancer 1970; 26: 780–7.
24. Hop WCJ, Werf-Messing BHP. Prognostic indexes for renal cell carcinoma. Eur J Cancer 1980; 16: 833–40.
25. Janssen CW Jr, Maartmann-Moe H, Lie RT. Preoperative prediction of extent and prognosis of gastric carcinoma by four serum proteins and erythrocyte sedimentation rate. Eur J Surg Oncol 1987; 13: 285–95.
26. Hannisdal E, Grøttum KA, Langmark F. Erythrocyte sedimentation rate as a prognostic factor in chronic lymphocytic leukaemia. Scand J Haematol 1986; 36: 253–7.
27. Hacene K, Desplaces A, Brunet M, Idereau R, Bourguignat A, Oglobine J. Competitive prognostic value of clinicopathologic and bioimmunologic factors in primary breast cancer. Cancer 1986; 57: 245–50.
28. Hannisdal E, Thorsen G. Regression analyses of prognostic factors in colorectal cancer. J Surg Oncol 1988; 37: 109–12.
29. Tubiana M, Henry-Amar M, Burgers MV, van der Werf-Messing B, Hayat M. Prognostic significance of erythrocyte sedimentation rate in clinical stages I–II of Hodgkin's disease. J Clin Oncol 1984; 2: 194–200.