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Specialist Interest Articles

Prognosis at Presentation of Small Cell Carcinoma of the Lung

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Prognostic factors in 411 patients with small cell lung carcinoma have been retrospectively analysed. Univariate analysis of continuous variables showed that prognosis was worse with deteriorating performance status, extensive disease, positive bone scan, increasing age, elevated total white cell count, alkaline phosphatase, lactate dehydrogenase, and decreased serum chloride and albumin. Low serum sodium was less clearly associated with poor survival. Cox multivariate regression showed that performance status, disease extent, age and raised lactate dehydrogenase and white cell count were independent prognostic factors. When disease extent was excluded from analysis, performance status, age, total white cell count, lowered serum chloride and raised lactate dehydrogenase were significant independent prognostic variables.
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INTRODUCTION

SMALL cell carcinoma of the lung (SCCL) is generally regarded as a systemic disease. Partly as a legacy of the period when radical radiotherapy was considered the only curative approach, pretreatment management has been to stage patients carefully. Despite the advent of systemic chemotherapy as the mainstay of therapy for all stages of disease, such treatment often means extensive interventional investigation when long-term survivors are few. Thus, simple prognostic indices are needed, from which survival can be anticipated and patients selected for particular treatment strategies. Performance status (PS) and disease extent have been identified as the most important prognostic factors [1] and alkaline phosphatase, serum sodium and serum albumin are additional independent predictors of survival [2]. We have used a similar design to confirm general applicability to other populations of patients with SCCL.

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PATIENTS AND METHODS

All 411 patients attending the Edinburgh Medical Oncology Unit between 1982 and 1988 were included and data at presentation were collected (age, sex, performance status, disease extent, basic haematology and biochemistry). These data have been assessed in a retrospective survival analysis. Staging investigations included full blood count, urea, electrolytes, lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase (AST), gamma glutamyl transferase, albumin and chest X-ray; liver ultrasound, bone scane or bone marrow aspiration were preferred if there was clinical suspicion of involvement. The patients were not treated homogeneously since four chemotherapeutic protocols were used over the period.

Eight-one patients received methotrexate 200 mg/m^2 as a 24 h infusion with folinic acid rescue and cyclophosphamide 1 g/m^2 every 3 weeks and CCNU 100 mg/m^2 (MCC) every 6 weeks for six courses followed by randomization either to no further treatment or up to 6 months of vincristine 1.4 mg/m^2 (days 1 + 8) plus procarbazine 100 mg/m^2 (days 1–14 orally), alternating monthly with methotrexate 40 mg/m^2 and cyclophosphamide 500 mg/m^2 intravenously (days 1 + 8), as maintenance chemotherapy. This maintenance therapy had no influence upon survival [3].

Table 1. *Log-rank results*

	No.	No. of deaths	Median survival (months)	*P* value
Age				
28–59	157	145	9	
60–65	120	108	8	0.03
66–79	134	124	6	
Extent of disease				
Limited	207	182	10	<0.001
Extensive	203	194	6	
Performance status				
0	73	66	10	
1	173	163	9	<0.001
2	107	101	6	
3	29	28	4	
Total white cells × 10^9 /l				
2–7.75	131	122	9	
7.76–9.75	130	117	9	0.03
9.76–25.30	132	120	7	
Lactate dehydrogenase (mmol/l)				
73–362	113	104	4	
363–512	110	101	7	<0.001
513–4465	125	115	6	
Albumin (mmol/l)				
25–37.5	80	73	6	
37.6–41.5	96	81	8	0.003
41.6–58.2	101	90	10	
Chloride (mmol/l)				
26–97	119	114	7	
98–101	114	102	7	0.05
102–119	122	111	9	
Alkaline phosphatase				
39–90	133	125	9	
91–130	124	111	9	0.04
131–1270	114	102	7	
Sodium (mmol/l)				
109–135	111	99	7	
136–139	131	124	8	0.06
140–147	133	118	9	
Gamma glutamyl transpeptidase				
10–30	45	39	8	
31–70	65	57	8	0.03
71–1461	43	39	6	
Neutrophils × 10^9/l				
1.5–5.49	45	40	10	
5.5–8.49	53	46	8	0.006
8.5–22.5	44	42	6	
Bone scan				
Normal	144	134	10	0.01
Abnormal/equivocal	71	65	7	

One hundred and twenty-eight patients received methotrexate 200 mg/m^2 over 24 h with folinic acid rescue, cyclophosphamide 1 g/m^2 and etoposide 120 g/m^2 or days 1–3 every 3 weeks for four courses (MCVP16). For 11 complete responders, high-dose intensification therapy with melphalan 140 mg/m^2 with autologous marrow rescue was given with subsequent radical radiotherapy to the mediastinum together with prophylactic cranial irradiation. A further 10 of these patients received radical mediastinal irradiation (four of whom had prophylactic cranial irradiation) but did not receive high-dose melphalan either from choice or from exclusion because of age.

One hundred and twenty-eight patients who were elderly or who presented with clinically obvious extensive disease and who were in poor general health (PS 2 or greater) received a palliative regimen of vindesine 3 mg/m^2 and etoposide 120 mg/m^2 on days 1–3 (16 received etoposide 360 mg/m^2 maximum 600 mg on day 1) every 3 weeks for six cycles (VVP16) [4]. A fourth group of 47 received drugs similar to the first group with additional doxorubicin (MACE) at 50 mg/m^2 every 3 weeks. The other 27 patients received various other cytotoxic combinations.

Statistics

The effect on survival of continuous variables was examined with the logrank test [5]. All variables that were significant at the 10% level were put into a forward step multiple regression analysis (Cox) [6]. All variables were checked for normality and transformed where appropriate into the natural log scale. The assumption of proportional hazards was tested for each variable by observing constant vertical differences (independent of time) between plots of estimates of the log of the integrated (cumulative) hazard function against time for different levels of each variable [7]. From the multivariate analysis, the size of the data set depended on which variables were included.

RESULTS

Survival for the whole group of patients was considered in relation to each continuous variable in isolation. The *P* value was greater than 0.1 for sex, site of extensive disease, haemoglobin, platelets, lymphocytes, erythrocyte sedimentation rate (ESR), AST and potassium. The other results are shown in Table 1. Results for albumin, gamma-glutamyl transferase and neutrophil count were not recorded in all patients. Extent of disease ($P < 0.001$), performance status ($P < 0.001$) and serum lactate dehydrogenase ($P < 0.001$) were the variables most strongly related to survival. Raised total white cell count and decreased chloride were inversely related to survival. Insufficient data were available for adequate analysis of differential white cell count.

Multivariate analysis

Cox's regression model showed that extensive disease, poor performance status, greater age, lactate dehydrogenase and total white cell count were independently adverse prognostic indicators (Table 2). The use of the categories examined and

Table 2. *Cox regression model on* 320 *patients*

Variable	Regression coefficient	Standard error	*P* value
(a) *With extent of disease*			
Limited/extensive disease (0=limited, 1=extensive)	0.56	0.12	<0.0001
Lactate dehydrogenase (log)	0.39	0.10	0.0001
Age (years)	0.02	0.01	0.002
Performance status (0,1,2,3)	0.21	0.07	0.004
Total white cell count (log)	0.45	0.18	0.01
(b) *Excluding extent of disease*			
Lactate dehydrogenase	0.52	0.10	<0.0001
Performance status	0.22	0.07	0.003
Age	0.02	0.07	0.01
Chloride	−0.02	0.01	0.02
Total white cell count	0.37	0.18	0.04

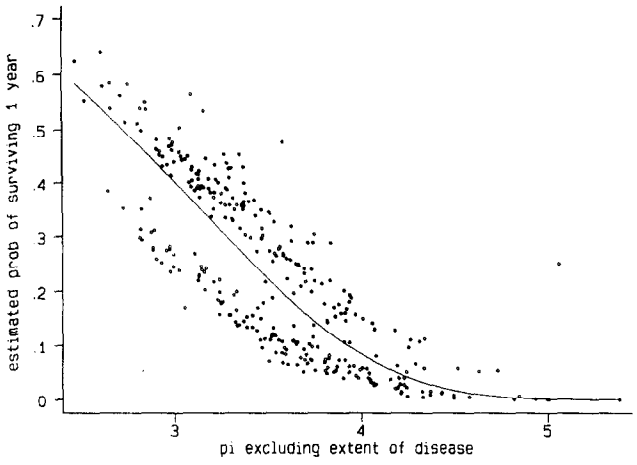

Fig. 1. Estimated probability of surviving 1 year for two Cox models. P_i = prognostic index for model excluding extent of disease. Line = model without extent of disease (Table 2b). Circles = probabilities based on model with extent of disease. Circles below line are mainly patients with extensive disease for whom "Cox 2b" model overestimates probability of surviving 1 year; circles above line are mainly patients with limited disease for whom "Cox 2b" underestimates probability of surviving 1 year.

limited disease have been useful in prognosis and have influenced modern management. These variables depend on time consuming, sometimes uncomfortable, and expensive procedures. A prognostic index that avoided such staging would be of great practical benefit. Thus we also confirmed an index that excluded extensive disease and limited disease from analysis. The result was that deteriorating performance status and increasing age, total white cell count and lactate dehydrogenase but decreasing serum chloride were then inversely related to prognosis (Table 2). In neither case was treatment a significant prognostic factor.

Figure 1 shows the estimated probability of surviving 1 year for the two Cox models. The probabilities are plotted against the prognostic index for the model excluding assessment of extent of disease. Most patients' survivals are close to the line so that disease extent assessment is uninformative. For about five patients (above the line) the non-availability of classification of disease extent results in an inadequate estimation of prognosis.

DISCUSSION

Although chemotherapy has improved the median survival of patients with SCLC further improvements in median and 2 year survival rates have not been substantial, despite increasingly aggressive therapies. In our group of 411 patients, several different regimens were used in populations that were believed to have different long-term survival. Nonetheless, in multivariate analysis where these differences were allowed for, treatment was not a significant prognostic factor. We therefore believe that there is useful prognostic information to be gained from studying the overall survival of these patients. Extensive disease and deteriorating performance status were confirmed as important adverse prognostic factors. The independent variables of poor prognosis in the Cox model were raised lactate dehydrogenase [8, 9], raised total white cell count and old age. Increased white cell count may reflect secondary bronchopulmonary infection and 20% of patients with a count over $11 \times 10^9/l$ died within the first 3 weeks of treatment. Infection may be a frequent contributory cause of early deaths associated with SCCL [3]. Unfortunately, insufficient data were available on the differential white cell count. The influence of age in our study might well reflect a more intensive approach to the care of younger patients with SCCL. Only Maurer and Pajak [10] have suggested that survival was inferior in their patients over 60 years of age.

Exclusion of extent of disease from regression analysis is important if clinical management and prognosis are to be based on indices that are simpler and cheaper than those in conventional staging of SCCL patients. In our analysis that excluded disease extent, low serum chloride became an independent adverse prognostic variable.

Three previous studies [2, 11, 12] have found low serum albumin to be associated with poor prognosis. Our univariate analysis indicated that this may be true but insufficient data were available for further analysis. In some reports, a poor prognosis is indicated by low serum sodium [2, 8, 9]. In limited disease, elevated serum AST [12], low bicarbonate [8] and low haemoglobin [9], were found to be of prognostic value.

Prognostic scoring based on clinical and biochemical findings has been proposed [2, 12] but there is no agreement on which factors should be used. Certainly the reduction of time-consuming, invasive and expensive investigations for SCCL would be advantageous. Such scoring should allow the identification of those patients for whom optimal conventional treatment may offer a real chance of long-term survival and, conversely, identify those for whom such treatment is inappropriate. Further development of such prognostic systems for clinical use may depend on the analysis of larger, pooled patient groups to identify variables of definite independent significance as well as on more meta-analysis [13].

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