Prognostic value of serum thymidine kinase, tissue polypeptide antigen and neuron specific enolase in patients with small cell lung cancer

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Summary  In a group of seventy patients with small cell lung cancer the prognostic value of serum tumour markers was determined. Thymidine kinase (TK), tissue polypeptide antigen (TPA) and lactate dehydrogenase (LDH) but not neuron specific enolase (NSE) correlated significantly with survival. Since all markers were strongly interrelated with each other and with the extent of disease, the combined determination of TK, TPA and LDH or the combination of disease extent and a marker yielded no more prognostic information than a single measurement of one of these variables.

Well established prognostic factors in small cell lung cancer (SCLC) are performance status (PS) and extent of disease (Maurer et al., 1981). Recently several groups have introduced biochemical data such as liver function tests, LDH, alkaline phosphatase, albumin haemoglobin, white blood cell count and bicarbonate to delineate prognostic subgroups in combination with PS and extent of disease or even as a replacement of extent (Souhami et al., 1985, Cerny et al., 1987). The prognostic significance of such biochemical data is probably either related to the tumourload and/or the site of metastases. The disadvantage of such an approach is that these data are an indirect reflection of the tumour. It seems more logical to investigate tumour derived products, which may give a direct estimation of the total body tumourload in a more refined way than the usual distinction between limited (LD) and extensive disease (ED). Several studies have been published on the prognostic value of tumour markers, but only few have compared the relative value of different prognostic factor (Deeus et al., 1987; Buccheri et al., 1987; Carney et al., 1982).

The purpose of this study was to determine the prognostic value of three tumour markers for response and survival in comparison with LDH, PS and extent of disease in a group of uniformly staged and treated patients.

Materials and methods

Patients

Pretreatment blood samples were obtained from 70 consecutive, previously untreated patients with a histological diagnosis of undifferentiated small cell carcinoma of the lung. Minimal staging procedures for all patients included physical examination, chest X-ray, computed tomography scan or ultrasound of the upper abdomen, bone scan and unilateral bone-marrow biopsy. Limited disease (LD) was defined as disease confined to one hemithorax including ipsilateral hilar, mediastinal lymph nodes, and supraclavicular lymph nodes and extensive disease (ED) as disease spread beyond the hemithorax including extension to the chest wall or to the contralateral lung. In 61 patients, chemotherapy consisted of doxorubicin 45 mg m⁻² intravenously (IV) on day 1, cyclophosphamide 1000 mg m⁻² IV on day 1, and etoposide 100 mg m⁻² IV on days 1, 3 and 5, repeated every 3 weeks for at least five cycles provided no progression occurred. The nine remaining patients were treated with various chemotherapy regimens in most instances including a combination of carboplatin or cisplatin and etoposide or ifosfamide. Disease response was evaluated according to standard WHO criteria after every two or five courses. Patients with rapidly progressive disease after one course of chemotherapy were documented as progressive disease. Survival was recorded from the start of treatment to death.

Marker assessment

NSE was measured with the Pharmacia NSE RIA test (Pharmacia AB, Uppsala, Sweden) as is described previously (Cooper et al., 1985). Serum concentrations above 12.5 ng ml⁻¹ were considered to be pathological. Serum TK activity was determined by the method of Gronowitz (Gronowitz et al., 1984) using a commercial radioenzymatic assay (Sangtec Medical Co, Bromma, Sweden) with ¹²⁵Iodo deoxyuridine as a substrate. TK levels above 5 U ml⁻¹ were considered as abnormal. TPA measurements were performed using a commercial kit (Prolifigen RIA Sangtec Medical Co, Bromma, Sweden). The cut-off level for normal TPA values was 100 U l⁻¹.

Statistical methods

The variables NSE, TK, TPA and LDH were log transformed before calculation of correlation coefficients and Cox regression analysis. Extent of disease was classified and coded as 1 = limited disease and 2 = extensive disease. Response was classified and coded as 1 = complete response, 2 = partial response and 3 = no response. The strength of the association between the markers, extent of disease, performance status, response and survival was expressed using linear correlation coefficients. However, Cox's regression analysis was applied to determine the relative importance of the prognostic factors on survival.

Results

Clinical characteristics are shown in Table I. Follow-up at time of analysis was completed for all patients but one, who was still alive 140 weeks after start of treatment. Pretreatment levels of serum NSE, TK and TPA could be determined in 69, 70 and 61 patients respectively. The percentage of patients with elevated markers in relation to the extent of disease is shown in Table II. Median NSE for patients with LD was 23 ng ml⁻¹ (range 8–132), and 71 ng ml⁻¹ (range 10–1000 ng ml⁻¹) for patients with ED. Median TPA for patients with LD was 5 U l⁻¹ (range 0.3–30), and 50 U l⁻¹ (range 7.5–500 U l⁻¹) for patients with ED. Median LDH for patients with LD was 1000 U l⁻¹ (range 200–7000 U l⁻¹), and 2000 U l⁻¹ (range 500–9000 U l⁻¹) for patients with ED. Median age for patients with LD was 62 years (range 36–83), and 63 years (range 47–86) for patients with ED.

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disease was intermarker correlation patients response (range LDH, 311 U
Extensive disease

9.4%)
Limited disease
29 (41%)
Extensive disease
41 (59%)
Response
complete response
27 (39%)
partial response
30 (43%)
stable disease
5 (7%)
progression
3 (4%)
non-evaluable
5 (7%)
Median survival all patients (weeks)
40 (range 0–143)
median survival limited disease
56 (range 13–140)
median survival extensive disease
30 (range 0–143)

Table II Percentage of patients with elevated markers in relation to the extent of disease

| Extent of disease | NSE TK | TPA | LDH | PS | Resp | Surv |
|------------------|-------|-----|-----|----|------|------|
| Limited disease  | 26 (90) | 11 (38) | 9 (36) |
| Extensive disease | 38 (95) | 28 (68) | 27 (79) |

Table III The correlation coefficients between the markers, LDH, according to performance score, response and survival

| Parameters | NSE TK TPA LDH PS Resp Surv |
|------------|-----------------------------|
| NSE        | 1                           |
| TK         | 0.57                        |
| TPA        | 0.71 0.61 1                 |
| LDH        | 0.72 0.70 0.84 1            |
| PS         | −0.42 −0.44 −0.51 −0.57 1   |
| Resp       | 0.31 0.58 0.49 0.57 −0.34 1 |
| Surv.      | −0.13 −0.37 −0.37 −0.35 0.25 −0.62 1 |

Abbreviations: NSE = log (neuron specific enolase); TK = log (thymidine kinase); TPA = log (tissue polypeptide antigen); LDH = log (lactate dehydrogenase); PS = performance score according to Karnofsky; Resp. = response; Surv. = survival; LD = limited disease; ED = extensive disease.

tates to only one organ site for example only liver metastases or only bone metastases (ED-1), and patients with metastases to more than one organ site (ED-2) (Table IV). In univariate analyses PS, disease extent, TK, TPA and LDH were all variables significantly correlated with survival. NSE on the contrary was not significantly correlated with survival (Table V). Since many of the above mentioned variables were interrelated, a multivariate analysis of the various factors has been performed in order to determine their relative prognostic importance. In the final model only TK remained as an significant prognostic factor. Addition of one of the other variables or extent of disease to a model with TK did not improve the fit of the model (P > 0.10). However due to the relative limited sample size and the observed standard error it could not be significantly shown that TK was a better prognostic factor than TPA, LDH or extent of disease.

Discussion

The evaluation of prognostic factors may serve different purposes such as choice of treatment, individual prognostication, comparison of different trials or trialarms and gathering knowledge about the heterogeneity and biological behaviour of the disease.

Figure 1 Scatter diagram of NSE and TPA.
The prognosis is dependent on the combined effects of prognostic factors and therapy, which therefore understandably are frequently linked. In case of chemotherapy the prognosis will be mainly determined by the total body tumourload, the fraction of chemotherapy-resistant cells, either predetermined or acquired, and the growth rate of the latter. Theoretically one or a combination of marker substances, which will reflect one of the above mentioned prognostic factors, would seem to be ideal. One of the prerequisites for such a marker would be that the amount, which is released or secreted per gram of tumour tissue, is independent of tumour heterogeneity or correlated with a prognostically important difference in biological behaviour.

In this study it was found that NSE, TK, TPA and LDH were significantly correlated with the extent of disease, with each other and with PS. TK, TPA and LDH but not NSE were also significantly correlated with survival. The former observations are in agreement with previous reports (Deuss et al., 1987; Buccheri et al., 1987; Gronowitz et al., 1986). The latter observation is not supported by the studies of Akoun et al. (1985) and Jorgensen et al. (1988) who showed that NSE is a significant prognostic factor for survival. The combined lack of correlation between NSE and both response and survival suggests that treatment related factors may be involved, i.e. that in contrast to the studies of Akoun et al. (1985) and Jorgensen et al. (1988) in our study a population of tumour cells is killed, which is correlated less with the serum NSE level. Approximately 85% of the patients in our study received a three-drug regimen consisting of cyclophosphamide, doxorubicin and etoposide. In the Danish study (Jorgenson et al., 1988) the patients received three different regimens, each of which contained at least six different drugs such as CCNU, cyclophosphamide, vincristine, etoposide, doxorubicin, cisplatin, vindesine and hexamethylmelamine. In the French study (Akoun et al., 1985) patients received four different drugs (cyclophosphamide, doxorubicin, vincristine and methotrexate). Although very different to prove it may be well that especially in the Danish study the six drugs killed a somewhat different population of tumour cells than the three drugs in our study. This may explain why serum NSE as a reflection of the tumourload is correlated with prognosis in one study and not the other.

TK, TPA, LDH and extent of disease all had significant prognostic capacity in the univariate analysis, however in the multivariate analysis it was shown that the combination of extent of disease and TK, TPA or LDH yielded no more prognostic information than the measurement of one of these parameters. Even a combination of the various markers didn’t improve upon the significance of a single marker. This latter observation may suggest that all these markers are picking out the same cells or bear the same relationship with the total tumourload.

Besides the fact that TK seems to be a good indicator of the total tumour mass it could have been assumed that there might be a relation between TK and the proliferative activity of the tumours of patients with small cell lung cancer since TK is involved in the process of DNA synthesis. Clinical evidence for the relation of TK and growth rate has been provided by the study of Greengard et al. (1985) in which it has been observed that TK concentrations of biopsy samples bear a quantitative inverse correlation to the volume doubling time of lung neoplasms as determined by tumour diameter measurements from sequential chest X-rays. However, if TK in SCLC relates with tumour growth rate this would most probably result in different responses to treatment for tumours based on their TK levels resulting in survival curves with different slopes (Shackney et al., 1978).

Survival curves calculated by the Kaplan-Meier method for different groups of patients based on their TK levels are depicted in Figure 2. Since the slopes of both depicted survival curves are identical this suggests that the prognostic capacity of TK is most probably entirely tumourload related.

In conclusion, in this study TK, TPA, LDH and extent of disease, but not NSE, proved to be valuable prognostic factors for prediction of survival. The prognostic significance of all these variables seems to be entirely tumourload related. Further studies including more patients are warranted to evaluate whether a single measurement of a marker can replace a crude distinction between LD and ED determined through a complicated staging procedure.
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