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FROM THE DEPARTMENT OF DISEASES OF THE CHEST, UNIVERSITY CENTRAL HOSPITAL, TURKU, FINLAND.

CONCOMITANT MONITORING OF SERUM NEURON-SPECIFIC ENOLASE AND CREATINE KINASE BB IN SMALL CELL LUNG CANCER

K. K. LIIPPO and T. TERHO

Abstract

Serum neuron-specific enolase (NSE) and serum creatine kinase isoenzyme BB (CK-BB) were measured in 43 small cell lung cancer (SCLC) patients. The overall sensitivity of NSE (>12.5 ng/ml) was 65%; in limited disease (LD) 48% and in extensive disease (ED) 100%. CK-BB was detected in 14 patients (32%); the sensitivity was 17% in LD and 64% in ED. During treatment NSE declined or stabilized to normal level in LD together with objective response in 75% (21/28), and rose again with progression in 28% (6/21). CK-BB fell to normal in all 5 patients with LD, in 3 of them with objective response. In ED elevated NSE and CK-BB declined to normal with objective response in 73% (8/11) and in 25% (2/8) of the evaluable patients respectively. We conclude that serum NSE is a potential marker for staging and response monitoring in SCLC, but that CK-BB gives additional information of limited value.

Key words: Small cell lung cancer, neuron-specific enolase, creatine kinase BB.

Neuron-specific enolase (NSE) has proved to be a valuable tool for the diagnosis of SCLC (1–3). The upper normal level for serum NSE is 12–13 ng/ml in many series (2–4), whereas higher values are mostly seen in patients with SCLC. The positive correlation between serum NSE concentration and the extent of SCLC indicates that serial evaluation of the enzyme can be a useful method in staging the disease and in monitoring the tumour response (3–5).

An isoenzyme of creatine kinase (CK-BB) is not detectable in normal lung tissue or serum in healthy adults (6). Although it is increased in a small number of non-malignant conditions, measureable concentrations have mainly been found in serum of SCLC patients (6, 7).

Since there is a need for more sensitive and specific markers for routine clinical use, we performed a prospective study to measure concomitantly two separate enzymes, serum NSE and serum CK-BB, to investigate if combined evaluation might provide greater accuracy for the staging of the tumour and monitoring the response.

Material and Methods

Altogether 196 paired serum samples with no visible hemolysis were collected from 43 patients with SCLC for NSE and CK-BB analysis at presentation, and sequentially prior to each course of chemotherapy every 3–4 weeks, and during the follow-up every 1–3 months. All the patients were males, current or ex-smokers, with a mean age of 63, 1 years. Of the patients 29 had localized and 14 extensive small cell lung cancer. Limited disease was defined as a tumour confined to one hemithorax and ipsilateral lymph nodes in the supraclavicular, hilar or mediastinal regions. The staging procedures included chest radiography, fiberoptic bronchoscopy with multiple biopsies, bone marrow aspiration, ultrasonography of upper abdomen, and bone and brain scintigrams if metastatic signs or symptoms existed. All the patients with Karnofsky performance status ≥ 60 were prescribed combination chemotherapy 6 times every 4 weeks or until progression. Radiotherapy was given for limited tumours. Tumour responses were evaluated according to the WHO criteria. The serum samples were kept frozen ($-20°C$) until assayed and analyzed, for NSE by double radioimmunoassay system (NSE RIA 100, Pharmacia Diagnostics AB, Uppsala, Sweden) (8), and for CK-BB by electrophoresis (Corning Medical and Scientific Limited, Essex, England). The normal level for NSE was defined as ≤ 12.5 ng/ml and CK-BB was regarded as abnormal if any activity in serum was detected.

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The statistical analysis was performed using Wilcoxon's two-sample test for non-parametric variables or Student's t-test. The results are expressed as mean values (±SD).

Results

Neuron-specific enolase

The mean serum NSE concentration was significantly higher ($p < 0.001$) in patients with extensive disease than in patients with limited disease (Table 1). Altogether 28 out of 43 patients (65%) had positive NSE (≥ 12.5 ng/ml); 14 out of 29 patients (48%) in the limited and all 14 patients in the extensive tumour group. If only one metastatic site was detected NSE was 143 ± 128 ng/ml ($n = 9$), and in patients with multiple extrathoracic lesions it was 171 ± 195 ng/ml ($n = 5$); the difference was not statistically significant.

Three different follow-up patterns of NSE and the tumour response of 28 patients with limited disease are shown in Table 2. Altogether 11 patients (38%) in the limited tumour group had objective response to treatment (complete or partial) associated with a decrease of NSE to the normal level, while in another 10 patients with objective response the normal pretreatment level remained unchanged. There were 4 patients with progressive disease and in one of them the NSE concentration rose over 12.5 ng/ml, but in 3 patients it remained or fell below this value in spite of clinical progression. During further treatment or follow-up, tumour progression was noted in 6 out of 21 patients who had had an objective primary response with a normal or stabilized NSE level. In 4 of these patients progression was observed concomitantly with elevation of NSE, in one case 4 weeks prior to and in another case 8 weeks after the clinical progression.

Out of 11 patients with extensive disease, progressive disease was noted in those 3 who had permanently high NSE. Elevated pretreatment NSE fell to normal in 8 cases, and this was associated with objective response in 6 cases, while no change was observed in 21 patients. Three out of 14 patients with extensive disease and one with limited tumour were not evaluable for response, due to early death.

Table 1

Concentration of neuron-specific enolase (NSE) and stage of small cell lung cancer at presentation

Tumour stage	n	Mean NSE (ng/ml)	±SD	Range
Limited	29	18.9	18	2.7–64.0
Extensive	14	152.0	149	18.2–492.0
Total	43	63.6	105	2.7–492.0

Table 2

Correlation between the best tumour response and the concentration of serum NSE in patients with limited small cell lung cancer (n = 28)

NSE	Tumour response		
	CR + PR	NC	PD
Falls < 12 ng/ml	11	0	1
Stabilizes < 12 ng/ml	10	3	2
Rises > 12 ng/ml	0	0	1
	21	3	4

CR = Complete response; PR = Partial response; NC = No change; PD = Progressive disease.

Creatine kinase

The pretreatment concentration of CK-BB was elevated in 14 out of 43 patients (32%). Nine of them (64%) had extensive tumours and the mean CK-BB in this group was 18.4 U/l (range 10–31); this represented 22% of the total CK activity in serum. In 5 patients with limited disease, the mean CK-BB was 7.9 U/l (range 6.0–9.7), representing 19% of the total CK. In Table 3 CK-BB is presented as the mean percentage of total serum CK. There was no significant differences between different tumour stages ($p > 0.05$).

During treatment, serum CK-BB declined to an undetectable level in all 5 patients with limited disease, and in 3 of them objective response was simultaneously observed. Elevated CK-BB remained high in 5 out of 9 patients with extensive disease, and all of them had tumour progression. In 3 more patients with normal, undetectable pretreatment levels (one with limited and two with extensive disease), CK-BB increased during treatment or late follow-up and in these patients clinical progression occurred. The increase of CK-BB was noted 2 months prior to and 1 and 2 months after the clinical signs of tumour spread respectively.

Neuron-specific enolase and creatine kinase

The combined analysis of these two enzymes is presented in Table 3. All 14 patients with positive CK-BB had

Table 3

Relation between stage of SCLC at presentation, different levels of NSE, and elevated value of CK-BB (CK-BB +)

	NSE (ng/ml)			
	0–12.5	>12.5–25	>25–50	>50
Limited	15	6	5	3
Extensive	0	3	1	10
Limited (CK-BB+)	0	0	4	1
Extensive (CK-BB+)	0	0	0	9

Table 4

Stage of small cell lung cancer and pretreatment findings concerning neuron-specific enolase (NSE) and creatine kinase BB (CK-BB). + marks elevated value and − normal value

	NSE+	NSE−
Limited disease		
CK-BB+	5	0
CK-BB−	9	15
Extensive disease		
CK-BB+	9	0
CK-BB−	5	0

also elevated NSE. There was a clear inconsistency between the enzymes in 14 cases; in 9 LD and in 5 ED CK-BB was 'false negative', with concomitant elevation of NSE (Table 4). The sensitivity of NSE in the limited stage was 45%, and in the extensive stage 100%. The sensitivity of CK-BB was 17 and 64% respectively. All the CK-BB positive patients had a moderately elevated pretreatment NSE level (>25 ng/ml) and in the subgroup of patients with marked elevation of NSE (>50 ng/ml) 71% of the CK-BB samples were positive.

Discussion

The aim of the present study was to improve the accuracy of the staging and response monitoring of SCLC by analyzing the isoenzyme BB of creatine kinase in combination with NSE. The results show that the mean concentration of NSE exceeded in two-thirds of patients the level of 12.5 ng/ml, which is in agreement with most previous observations (4, 9), and it was increased over this crucial level in all patients with extensive disease. This observation would be helpful in suspected cases of clinically silent metastases or tumour progression, but for clinical decision it is less reliable. In the present series there still remains an overlap in the distribution of NSE values between different stages; there was one patient with highly positive NSE (over 50 ng/ml) in the limited group, although this concentration is usually indicative of metastatic disease. Esscher et al. (3), moreover, reported even larger number of such cases (22%), whereas the number of patients in the study by Cooper et al. (4) was 13%, which is in agreement with our observations. On the other hand, there are always some patients with confirmed extensive SCLC combined with relatively low NSE level (<25 ng/ml) (9, 10). In the present series there were 3 such patients (21%). The combined measurement of CK-BB and NSE would give some support in staging of the disease, since in the present study CK-BB positivity was observed in 10 out of 14 patients with concurrent NSE concentration over 50 ng/ml, 9 of whom belonged to the extensive group. The quantitative analysis of CK-BB seems to provide no further information, although the number of patients in this particular group was small.

False staging is possible even for experienced clinicians, which usually means underestimation of the number of cases with extensive disease. In the present study 8 patients were staged primarily as limited disease, and all of them had NSE over 25 ng/ml at presentation. In general an increase of NSE of the magnitude should strongly indicate the presence of extensive tumour and a large tumour burden (3), especially if CK-BB is simultaneously elevated (11), which was the case in 5 of our patients. Even we cannot rely on the indications given by elevated markers alone, they may strengthen the suspicion of extensive tumor prompted by clinical symptoms. Such clinical indicators of metastases are sometimes more accurate than routine staging with radionuclides, e.g. bone scanning (12). In favour of tumour markers, Gazdar et al. (7) and Coolen et al. (6) have found consistent elevation of CK-BB in serum of patients with extensive SCLC, and it may even be useful in the primary diagnosis of SCLC. The combination of CK-BB with NSE analysis might therefore sometimes be very sensitive, and give additional information for detection of silent metastases. For clinical routine, however, the combined use of the two markers does not seem to give essentially more information than NSE alone.

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Corresponding author: Dr Kari Liippo, Department of Diseases of the Chest, University Central Hospital of Turku, Paimion Sairaala, SF-21540 Preitilä, Finland.

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