ProGRP and NSE in Therapy Monitoring in Patients with Small Cell Lung Cancer

EWA WÓJCIK[1], JAN K. KULPA[1], BEATA SAS-KORCZYŃSKA[2], STANISŁAW KORZENIOWSKI[2] and JERZY JAKUBOWICZ[2]

Departments of [1]Clinical Biochemistry, and [2]Radiotherapy, Center of Oncology – M.Skłodowska-Curie Memorial Institute, Cracow Division, Poland

Abstract. *The usefulness of serum pro-gastrin-releasing peptide (ProGRP) as a tumor marker in patients with small cell lung cancer has recently drawn the attention of many research centers. The aim of the study was the evaluation of ProGRP, neuron-specific enolase (NSE), soluble fragment of cytokeratin 19 (CYFRA 21-1) and lactate dehydrogenase (LDH) levels at the time of diagnosis and during chemo- and radiotherapy of small cell lung cancer patients with limited disease (SCLC-LD). The studies were performed on a group of 64 patients with SCLC-LD who had received no prior therapy. All the patients were given the same treatment regimen. ProGRP, NSE, CYFRA 21-1 and LDH were measured before each course of chemotherapy and then at 3 and 6 months after the end of treatment. Prior to therapy, elevated levels of ProGRP, NSE, CYFRA 21-1 and LDH were found in 79.7% , 57.8% , 23.4% , and 12.5% of the patients respectively. Before the second chemotherapy course, all the tumor marker levels except LDH decreased significantly in comparison with the pretreatment concentrations. However, only ProGRP levels showed a progressive drop during consecutive courses of therapy, while NSE and CYFRA 21-1 fluctuated within reference ranges. When the study group was divided with respect to the effect of treatment evaluated six months from its termination, significant differences in ProGRP levels were found between both subgroups throughout all therapy and follow-up, except for the fifth course of chemotherapy. Differences in NSE levels were only significant for the first two courses and follow-up. Univariate analysis showed significant relationships between disease-free survival and the initial levels of NSE and CYFRA 21-1 as well as between overall survival and prophylactic cranial irradiation (PCI) and the initial ProGRP, NSE and CYFRA 21-1 levels. Changes of ProGRP level seem to be more precise than NSE as a tool for monitoring therapy in SCLC patients with limited disease, but for prediction of relapse, in addition to NSE determinations of ProGRP seem to be optimal.*

Correspondence to: Professor Dr. hab. Jan Kulpa, Department of Clinical Biochemistry, Center of Oncology M.Skłodowska-Curie Memorial Institute, st. Garncarska 11, 31-115 Cracow, Poland. Tel: +48 0124228760, Fax: +48 0124293262, e-mail: z5jkulpa@cyf-kr.edu.pl

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Small cell lung cancer (SCLC) is an aggressive and rapidly growing neoplasm, often presenting with metastatic disease in regional lymph nodes or distant organs at the time of diagnosis. Neuroendocrine differentiation of SCLC is considered to be an important feature of this disease and may explain its high sensitivity to chemotherapy and radiotherapy (1, 2). Reliable tumor markers are needed to check the effectiveness of therapy in disease monitoring and moreover provide additional information about survival. A number of serum components have been proposed as markers of the extent of disease and of the clinical response to cytotoxic therapy in patients with SCLC. Among those, neuron specific enolase (NSE) is generally accepted as a marker in the diagnosis and therapy monitoring of SCLC. Moreover, it has been found that the levels of this marker have prognostic value (3). Although the diagnostic sensitivity of this marker in SCLC patients with limited disease (SCLC-LD) is 40-60% , the diagnostic specificity is rather limited, due to a relatively high false-positive rate in patients with non-malignant lung disease and non-small cell lung cancer as well as some neuroendocrine and brain tumors (4-9). Thus a more reliable tumor marker for the diagnosis of SCLC patients, especially those with limited disease, is required. Several other neuroendocrine molecules have been studied as tumor markers in SCLC, such as chromogranin A, bombesin and synaptophysin and in addition to NSE, analysis of soluble fragment of cytokeratin 19 (CYFRA 21-1) or lactate dehydrogenase (LDH) has been performed (7). In more recent years, studies have been focused on gastrin-releasing peptide (GRP), a bombesin-like peptide which is present in the fetal lung and the adult human gastrointestinal and

respiratory tract as well as the central nervous system (10). It is also produced and secreted by SCLC cells. However, due to its very short half-life, GRP cannot be used in laboratory practice. Miyake *et al*. demonstrated that the serum precursor peptide (31-98) of GRP (ProGRP), which is produced in equimolar proportion to GRP, is stable in serum and may be a reliable tumor marker for identifying SCLC and has received attention at many research centers (1, 11-17).

The diagnostic sensitivity and specificity of ProGRP has been found to be higher than that of NSE, especially in early stages of SCLC (8). Moreover, preliminary results have suggested the utility of ProGRP concentration in the follow-up of SCLC patients (13). However, there are only a few reports of the usefulness of ProGRP as a marker for treatment monitoring and detection of relapses, and data on its prognostic value are rare and controversial (8, 13).

The aim of the present study was the evaluation of ProGRP, NSE, CYFRA 21-1 and LDH levels at the time of diagnosis and during chemo- and radiotherapy of SCLC-LD patients and of the utility of these tumor markers in the assessment of prognosis.

Materials and Methods

Sixty-four SCLC-LD patients who had received no prior therapy, were enrolled in this study. They were referred to the Center of Oncology, M. Skłodowska-Curie Memorial Institute, Cracow Division between 2000-2005. Clinical staging was based on the results of physical examination, chest radiography, computed tomography, bone scintigraphy and bone marrow aspiration. The planned treatment involved five courses of chemotherapy according to an EP-regimen (etoposide, cisplatin) with thoracic irradiation after the second course, and prophylactic cranial irradiation (PCI) after the fourth course of EP. However, only 48 out of the 64 patients received the full schedule of therapy because 16 were disqualified from PCI due to their bad response to treatment or other complications.

To detect signs of relapse, the patients regularly underwent physical examination. Chest radiography was performed before each course of chemotherapy and during follow-up. Computer tomography of the chest was also carried out after the end of treatment and six months later, at the time of restaging. The overall response to treatment was analyzed according to the World Health Organization criteria. Local recurrence and dissemination were found in 22 patients six months after the end of treatment.

Blood samples were obtained by venous puncture before each course of chemotherapy as well as three and six months after the end of treatment. The sera were stored at –25˚C until used. Creatinine levels were examined in all the patients at each point of the study, in order to disqualify those with abnormal ProGRP levels due to renal failure. The tumor markers NSE and CYFRA 21-1 were measured by commercial electrochemiluminescence immunoassay (ECLIA) using ELECSYS 2010 analyzer and reagent kits (Roche Diagnostics, Mannheim, Germany). ProGRP was determined by a commercial sandwich ELISA (Advanced Life Science Institute, Saitama, Japan). The LDH activity was measured by a kinetic spectrophotometric method in a Hitachi Model 912 biochemical analyzer (Roche Diagnostics). The cut-off values were decided on the basis of determination of these parameters in a reference group of healthy people and patients with benign lung disease as levels corresponding to the 95% ; percentile and were: NSE, 24.7 μg/L; CYFRA 21-1, 3.31 μg/L; ProGRP, 49.0 ng/L; and LDH, 450 IU/L. For the evaluation of tumor marker change kinetics, the ratio of the level before consecutive courses of treatment to the initial level was calculated for each patient.

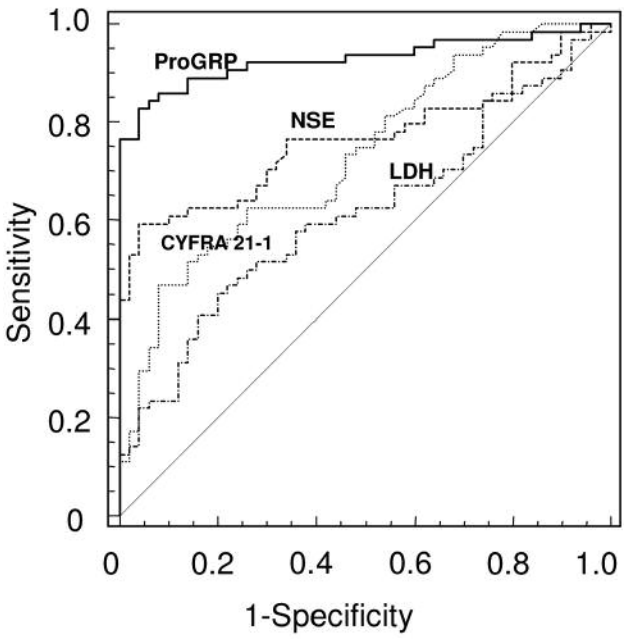

Figure 1. *ROC curves analysis in SCLC-LD versus. reference group. (AUC: ProGRP – 0.929±0.024; NSE – 0.766±0.044; CYFRA 21-1 – 0.732±0.052; LDH – 0.616±0.046). SCLC-LD: Small cell lung cancer, limited disease; ProGRP: precursor of gastrin releasing peptide; NSE; neuron specific enolase; CYFRA 21-1: soluble fragment of cytokeratin 19; LDH: lactate dehydrogenase.*

The non-parametric Kruskal-Wallis test was applied to assess the significance of differences between the studied subgroups or particular courses of treatment. Pearson's correlations were calculated for evaluation of the relationship between the levels of the tumor markers. Survival analysis was performed by the Kaplan-Meier method. The values best differentiating between the two groups in relation to survival were calculated using the log-rank test. Multivariate analysis by Cox's proportional hazards model was used to establish the association between various prognostic factors and survival.

Results

ROC curve analysis revealed that ProGRP was better than NSE and the remaining tumor markers in SCLC patients with limited disease. The area under the ROC curves (AUCs) of ProGRP was significantly greater than that for NSE, CYFRA 21-1 and LDH (Figure 1). Before therapy, the frequency of elevated ProGRP levels was significantly higher than that of NSE, and elevated levels were found in 79.7%

Table I. *Changes of tumor marker concentrations during therapy and follow-up in SCLC-LD.*

Therapy	ProGRP (ng/l)	NSE (μg/l)	LDH (U/l)	CYFRA 21-1 (μg/l)
1st Course				
Median	298.27	30.22	318.4	2.22
range	5.92-3280.70	3.05-270.70	203.1-2554.0	0.81-21.78
elevated results	79.7%	57.8%	12.5%	23.4%
2nd Course				
Median	86.06[a]	10.16[a]	313.05	1.59[a]
range	5.1-1703.3	3.59-67.85	203.1-528.0	0.11-8.79
elevated results	67.2%	6.3%	3.1%	6.3%
3rd Course				
Median	42.30[b]	8.86[b]	279.8[b]	1.45
range	4.7-948.17	2.36-21.25	203.6-539.3	0.26-3.60
elevated results	43.8%	0%	3.1%	1.6%
4th Course				
Median	29.15[c]	8.14	322.60[c]	1.39
range	3.13-339.66	4.48-29.96	227.5-506.1	0.10-3.27
elevated results	27.1%	1.7%	3.4%	0%
5th Course				
Median	22.02	8.37	336.10	1.48
range	2.68-260.66	2.29-98.84	240.9-633.6	0.52-2.93
elevated results	26.9%	1.9	3.8%	0%
C (3 m)				
Median	18.21	7.54	316.90	1.56
range	3.62-561.87	3.07-54.27	172.1-750.0	0.44-3.05
elevated results	17.4%	6.5%	8.7%	0%
C (6 m)				
Median	36.54[d]	7.52	309.05	1.53
range	4.50-1735.2	3.49-274.60	223.4-949.4	0.65-3.92
elevated results	42.4%	11.8%	14.7%	8.8%

$p<0.05$-significant differences; [a]between 1st and 2nd course of chemotherapy; [b]between 2nd and 3rd course of chemotherapy; [c]between 3rd and 4th course of chemotherapy; [d]between three [C (3 m)] and six [months after the end of treatment (6m)].

and 57.8% of the patients, respectively ($p=0.0076$). Increased ProGRP and/or NSE levels appeared in 85.9% of patients. Elevated CYFRA 21-1 and LDH were found in relatively low percentages of patients, 23.4% and 12.5% respectively. A strong correlation was observed between NSE and LDH (r=0.624, $p=0.0001$) and significant but rather weak relationships between the initial levels of: NSE *vs*. ProGRP (r=0.373, $p=0.002$), and NSE *vs*. CYFRA 21-1 (r=0.392, $p=0.001$), as well as a lack of correlation between ProGRP and LDH or CYFRA 21-1.

The concentrations and positive ratios of the tumor markers in the SCLC-LD patients, both before each course of chemotherapy and at the time of restaging, are given in Table I. Before the second chemotherapy course, all the tumor marker levels except for LDH had decreased significantly in comparison with pretreatment concentrations. The kinetics of ProGRP and NSE level changes were only similar after the first course of chemotherapy (Figure 2). While ProGRP levels during consecutive courses of therapy fell throughout the entire period, the NSE, CYFRA 21-1 and LDH levels fluctuated within reference ranges.

At the time of restaging, six months from the termination of therapy, complete remission was found in 65.6% of the patients. When the study group was divided with respect to the effect of treatment, significant differences in NSE concentration were observed between the remission and progression groups only before first and second courses of chemotherapy, and at the time of restaging, three and six months later (Figure 3). Significant differences in the ProGRP levels were found between both subgroups throughout the whole therapy, except for the fifth course of chemotherapy, and during follow-up (Figure 4).

In the group of patients with progression appearing at six months after the end of therapy, the frequencies of elevated NSE and ProGRP pretreatment levels were very similar, but in the subsequent courses of treatment, the percentages of elevated ProGRP levels remained significantly higher than those for NSE (Figure 5A). The patients with remission presented a significantly higher percentage of elevated ProGRP levels prior to therapy, compared to NSE. Moreover, in subsequent courses of treatment, the frequency of elevated ProGRP concentrations slowly decreased, while no elevated NSE levels were seen (Figure 5B).

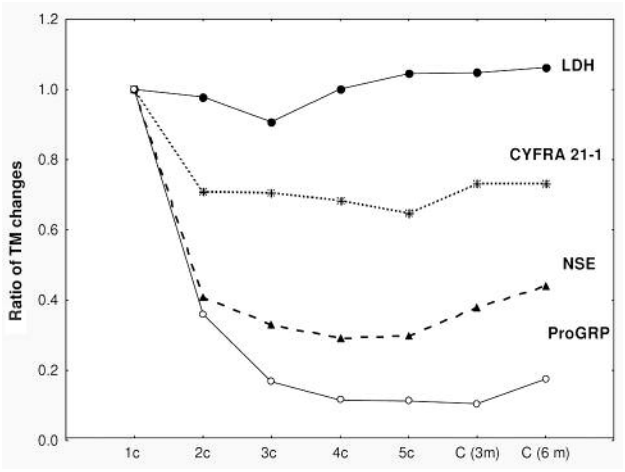

Figure 2. *Ratio of tumor marker (TM) changes during therapy and follow-up. c: chemotherapy course; C(m): control examinations: three and six months after the end of treatment.*

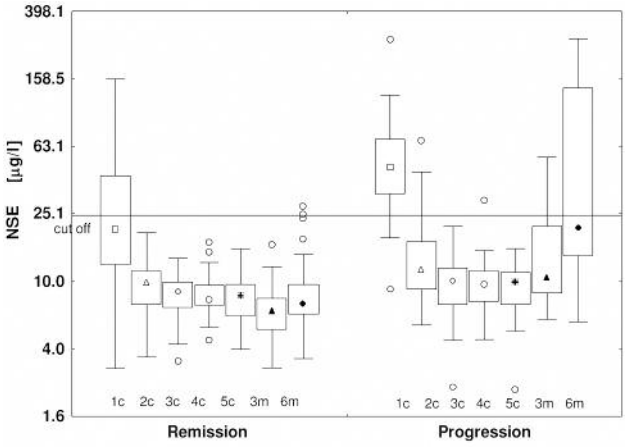

Figure 3. *Differences in NSE levels depending on the effect of treatment (remission vs. progression groups; 1st course: p=0.0005, 2nd course: p=0.019, 3rd course: N.S., 4th course: N.S., 5th course: N.S; during follow-up 3m: p=0.0001 and 6 m: p=0.003).*

The univariate analysis showed significant relationships between disease-free survival and both pretreatment NSE and CYFRA 21-1 concentrations and also between overall survival and prophylactic cranial irradiation as well as pretreatment ProGRP, NSE and CYFRA 21-1 levels (Table II and Figure 6, 7). Moreover, patients with elevated pretreatment ProGRP and NSE levels represented a group with especially poor prognosis (Figure 8). The multivariate analysis confirmed that in the group of SCLC-LD, no prophylactic cranial irradiation and elevated pretreatment NSE were independent, unfavourable prognostic factors (RR=4.22, CI: 1.89 – 9.43, p=0.0005 and RR=3.11, CI: 1.44 – 6.64, p=0.0036 respectively).

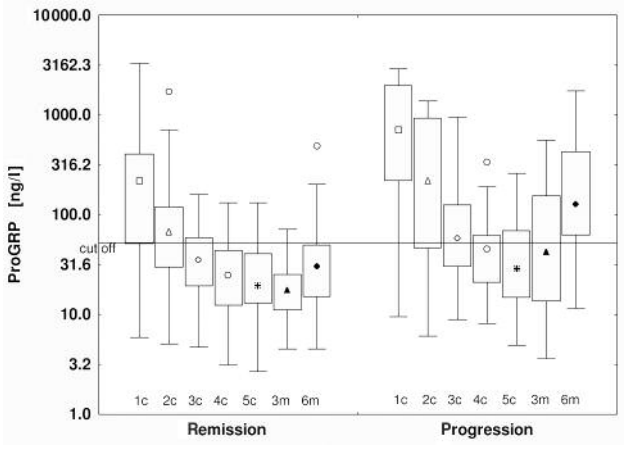

Figure 4. *Differences in ProGRP levels depending on the effect of treatment (remission vs. progression groups; 1st course: p=0.004, 2nd course: p=0.006, 3rd course: p=0.038, 4th course: p=0.040, 5th course: N.S; during follow-up 3m: p=0.033 and 6 m: p=0.020).*

Discussion

The presented study performed in a group of SCLC-LD patients confirmed earlier reports, as at similar specificity the diagnostic sensitivity of ProGRP was significantly higher than NSE. Whereas Okusaka *et al.* (13) showed that ProGRP and NSE levels in untreated patients with SCLC were poorly correlated, a weak but significant relationship between both markers was found in the present study. However, it seems that these tumor antigens are mostly independent of each other. In the opinions of some investigators, determinations of both markers may be helpful in establishing a diagnosis of SCLC in patients with lung tumors of unknown origin (16).

Most authors emphasize the excellent relationship between NSE changes and the clinical evaluation of response to therapy. However, the majority of them compared only the results before and at the end of treatment, rather than analyzing marker level changes during chemotherapy (13, 18-20). Similarly to Harding *et al.* (21), the normalization of initially elevated NSE levels was observed after the first course of chemotherapy in more than 90% of the patients in present study. Although it has been suggested that early normalization of serum NSE may reflect the biological therapeutic effect associated with higher percentages of complete response and better survival, it is unlikely that after the first course of chemotherapy so many genetically unstable and potentially drug-resistant cancer cells could be eliminated (22, 23). Slow changes in ProGRP levels which occur during chemotherapy seem to be more closely related to the clinical status of the patients, their reaction to treatment and a gradual reduction of cancer cells by the cytotoxic treatment. This observation was in agreement with the results of Yamaguchi *et al.* who showed

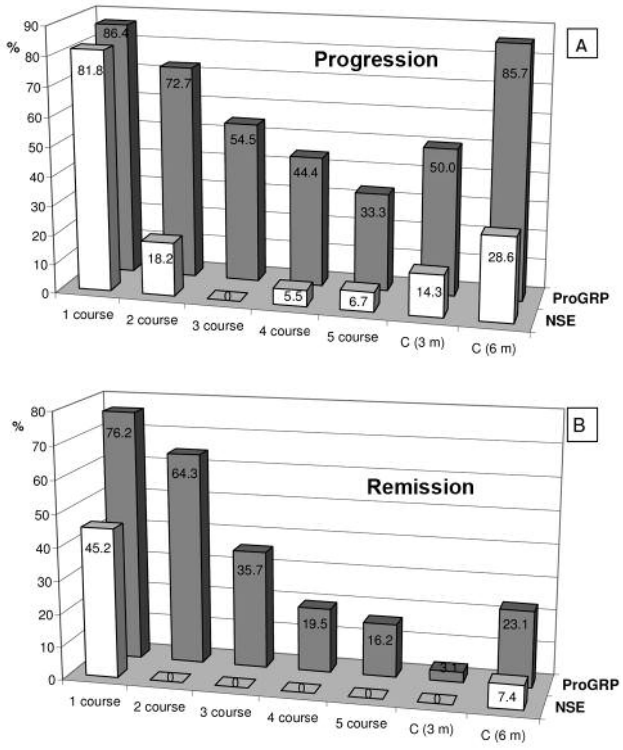

Figure 5. *Frequency of elevated ProGRP and NSE levels during therapy and follow-up in the group of patients with progression (A) and remission (B). course: chemotherapy course; C(m): control examinations: three and six months after the end of treatment.*

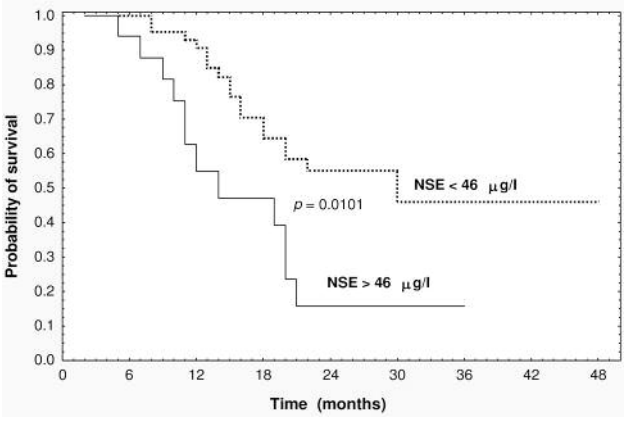

Figure 6. *Probability of SCLC-LD overall survival depending on the initial NSE level.*

that in SCLC patients, changes in the serum level of ProGRP were well correlated with therapeutic response (24). The different behaviour of ProGRP and NSE levels during treatment may be caused by various characteristics of these markers. ProGRP is a parahormone distributed not only in some neuroendocrine pulmonary cells, or

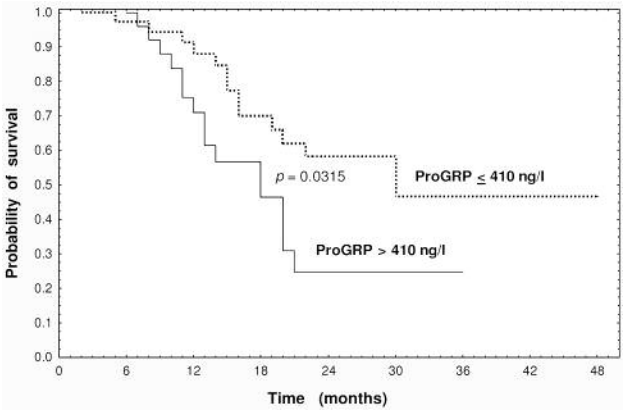

Figure 7. *Probability of SCLC-LD overall survival depending on the initial ProGRP level.*

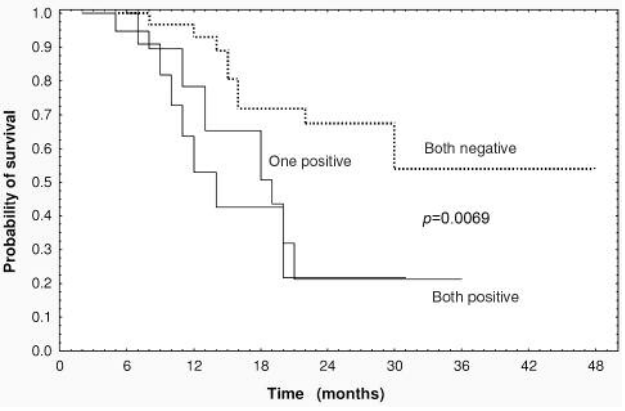

Figure 8. *Probability of SCLC-LD overall survival depending on the pretreatment ProGRP and NSE levels.*

Table II. *Univariate analyses of prognostic factors in SCLC-LD.*

			Disease-free survival		Overall survival	
Parameter	Variant	N	Median (months)	*p*-Value	Median (months)	*p*-Value
PS*	≥80	39	10	N.S	25.0	N.S
	<80	25	7		20.0	
PCI	Yes	48	14.5	0.030	27.0	0.0032
	No	16	3.0		13.0	
ProGRP [ng/l]*	≤410.0	38	16.5	N.S	27.0	0.0315
	>410.0	26	6.0		18.0	
NSE [µg/l]*	≤46.0	48	16.0	0.0259	26.0	0.0101
	>46.0	18	4.0		13.0	
LDH [U/l]*	≤380	43	10.0	N.S	21.0	N.S
	>380	21	7.0		19.0	
CYFRA 21-1 [µg/l]*	≤3.5	54	13.0	0.0098	23.0	0.0113
	>3.5	10	1.0		11.0	

PS: performance status (Karnofsky scale); PCI: prophylactic cranial irradiation. *Pretherapy values.

neighbouring cells, but which is also able to play an important role as an autocrine growth factor (10). This may explain its relatively elevated serum concentration before therapy and gradual decrease during treatment. Observations of changes of NSE levels, a glycolytic isoenzyme participating in cell anaerobic energy turnover, during treatment are divergent. It cannot be excluded that its production and release in the circulation can be quickly inhibited by cytotoxic drugs and the presented results may be seen as reflecting this mechanism. However, in contrast, Vogelzang *et al*. observed an increase of NSE during the first chemotherapy course and explained it as a consequence of biological tumor lysis syndrome (25).

In patients with progression, the high frequency of elevated ProGRP levels at the time of restaging may indicate the usefulness of this marker in the prediction of viable residual tumor after treatment. In this respect, ProGRP seems to more reliable than NSE (8, 13).

Many data emphasize the value of NSE in the detection of relapses and prediction of disease progression (5, 18, 19). The presented results are not in contradiction with those findings. The results of univariate analysis revealed a relationship between disease-free and overall survival and NSE levels prior to therapy, whereas the pre-therapy ProGRP levels correlated only with the overall survival. Moreover, a significant relationship was observed between the disease-free survival and pre-therapy CYFRA 21-1 levels that was in agreement with the findings of others in regard to the utility of this marker for the selection of SCLC patients with especially poor prognosis (26, 27). The prognostic value of initially elevated NSE in SCLC-LD patients was confirmed by the finding that it is one of the independent, unfavourable prognostic factors, while the relationship between ProGRP level and survival was not so marked and needs further study.

Conclusion

Changes of ProGRP level seem to be more precise than those of NSE as a tool for monitoring therapy and, together with NSE, determinations of ProGRP allow more reliable prediction of relapses and assessment of prognosis in SCLC-LD patients.

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