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Original Article

Pre-treatment and treatment-Induced Neuron-specific Enolase in Patients with Small-Cell Lung Cancer: An Open Prospective Study

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ABSTRACT

Background: Neuron-specific enolase (NSE) is the most sensitive tumour marker for small-cell lung carcinoma (SCLC) at the time of diagnosis. The main purpose of this study was to review the usefulness of serum NSE level as a prognostic factor in patients with SCLC and to determine the correlation between the NSE level and the stage of disease and response to chemotherapy.
Methods: In this prospective study, patients with SCLC were evaluated for response to chemotherapy, survival without disease progression, and overall survival. The end point was designated at patient death due to SCLC. NSE assays were performed before and after completion of chemotherapy.
Results: Sixty-five patients were included in study. NSE levels were significantly higher in patients who died of SCLC. The pre-treatment NSE levels in patients who responded to treatment were significantly lower. The post-treatment NSE levels were not significantly correlated with response to chemotherapy, progression-free survival, overall survival, and prognosis of patients. Change in the NSE level between the pre- and post-treatment periods was not significantly correlated with response to treatment, progression-free survival, and overall survival.
Conclusions: NSE levels might not be related with the stage of the disease. However, a low pre-treatment NSE level might be used in predicting good response to chemotherapy in patients with SCLC. The post-treatment serum NSE levels and the rate of change between pre- and post-treatment serum levels of NSE were not related with response to chemotherapy, progression-free survival, and overall survival.

Valores pretratamiento e inducidos por el tratamiento de enolasa específica de neurona en pacientes con cáncer de pulmón microcítico: estudio prospectivo, abierto

Palabras clave:
Carcinoma de pulmón microcítico
Enolasa específica de neurona
Quimioterapia
Respuesta al tratamiento
Supervivencia
Progresión

RESUMEN

Fundamento: La enolasa específica de neurona (EEN) es el marcador tumoral más sensible para el carcinoma de pulmón microcítico en el momento del diagnóstico. El objetivo del presente estudio fue revisar la utilidad de sus valores séricos como factor pronóstico en pacientes con este cáncer y determinar la correlación entre los valores y el estadio de la enfermedad y la respuesta a la quimioterapia.
Métodos: En este estudio prospectivo, se evaluaron pacientes con carcinoma de pulmón microcítico para su respuesta a la quimioterapia, supervivencia sin progresión de la enfermedad y supervivencia global. El criterio de valoración se designó como la muerte del paciente debida a la enfermedad. Los análisis de EEN se efectuaron antes y después de completar la quimioterapia.

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Resultados: Se incluyeron en el estudio 65 pacientes. Los niveles de EEN fueron significativamente más altos en los pacientes que fallecieron de la enfermedad. En pacientes que respondieron al tratamiento los valores pretratamiento fueron significativamente más bajos. Los valores postratamiento no se correlacionaron significativamente con la respuesta a la quimioterapia, supervivencia libre de progresión, supervivencia global y pronóstico de los pacientes. El cambio de los valores de EEN entre el intervalo pre y postratamiento no se correlacionó significativamente con la respuesta al tratamiento, supervivencia libre de progresión y supervivencia global.

Conclusiones: Es posible que los valores de EEN no guarden relación con el estadio de la enfermedad. No obstante, en pacientes con carcinoma de pulmón microcítico, en la predicción de una respuesta apropiada a la quimioterapia pueden usarse unos valores bajos previos al tratamiento. Los valores séricos postratamiento y la tasa del cambio entre los valores pre y postratamiento no se relacionaron con la respuesta a la quimioterapia, supervivencia libre de progresión y supervivencia global.

Background

Small cell lung cancer constitutes 15-20% of cases of lung carcinoma, it is a different entity to non-small cell lung cancer, characterised by rapid growth, early metastasis and a satisfactory response to chemotherapy.[1]

Although progress has been seen with combination chemotherapy, patients with this cancer continue to have a poor prognosis, especially those with disseminated disease. Since the 80s, researchers have paid attention to the factors that could be useful in predicting response to treatment and survival.[2] Significant factors for prognosis in this type of cancer are sex, extension of disease, general condition, weight loss, haemoglobin values, white blood cell and platelet counts, and concentration of lactate dehydrogenase and neuron specific-enolase (NSE[3]). NSE is a glycolytic enzyme that is present almost exclusively in neurons and neuroendocrine cells.[4] It is the most sensitive tumour marker for this cancer at the moment of diagnosis.[5-7]

The aim of this study was to review the usefulness of serum NSE values before and after treatment as prognostic factors in patients with small cell lung cancer and to determine the relation of this marker with stage of disease and response to chemotherapy. Furthermore, we also investigated the association of survival with the difference in pre and post-treatment NSE serum values, which has not been done before.

Method

Patients

In this prospective study we included patients with small cell lung cancer confirmed by histopathology who had been diagnosed between July 2007 and December 2008 in the Department of Thoracic Diseases of the Izmir Dr. Suat Seren Thoracic Diseases and Surgery Training and Research Hospital. The study protocol was approved by the local ethics committee of the institution. All patients read, approved and signed an informed consent form.

All patients without a defined disease stage or who had not received chemotherapy were excluded from the study. The diagnosis of disease extension in all patients in the study was performed using a CT with contrast enhancement, abdominal US, bone scintigraphy with CT^{99} and cranial CT with contrast enhancement or cerebral magnetic resonance. Systematic laboratory tests were also carried out, including a biochemical counts and blood count. At the time of diagnosis the following data was registered: date, sex, age, general condition score (0-4) of the Eastern Cooperative Oncology Group (ECOG[8]), smoking history (pack year), clinical stage (disseminated or regional disease[9]) and locations of metastasis.

Modes of Treatment

All patients received 4-6 cycles of chemotherapy with platinum derivatives at 21 day intervals. Etoposide was administered (100mg/m^2 on days 1, 2, and 3), combined with cisplatinum (75mg/m^2 on day 1) or carboplatinum AUC6 (carboplatinum [mg] = 6.0 $\times$ [glomerular filtration rate + 25] on day 1). Patients were assessed by physical exam, questions were asked about their symptoms, and systematic laboratory tests were performed (biochemical and haematological counts) before each chemotherapy cycle.

For radiotherapy a medical linear accelerator was used (6 MeV LINAC [Saturne 43®, General Electric, France]). A total of 46-50Gy of radical radiotherapy were applied to the mediastinum in patients with a complete response to chemotherapy. Patients who presented a partial response were administered a total of 46Gy to the mediastinum and a dose of 2Gy/day was applied to the tumour, and additional radical radiotherapy, a dose of 10Gy (reinforcement dose), was applied to the tumour. Although in 38 patients radical radiotherapy was started sequentially, in 6 patients it was begun simultaneously with the second cycle of chemotherapy. After chemotherapy and radical radiotherapy, prophylactic cranial irradiation with a dose of 110 $\times$ 250cGy was applied in patients who had obtained a complete response.

Response to Treatment and Follow-up

Patients were assessed by means of a chest CT to determine response to treatment after 2, 4 and 6 courses of chemotherapy. From the radiological point of view, it was considered that complete disappearance of a lesion was a 'complete response', a 50% reduction in size was considered a 'partial response', a reduction of less than 50% or growth that was less than 25% of the lesion was considered 'stable disease', and growth greater than 25% was considered 'progressive disease'.[10]

During follow-up, all patients were assessed by means of a chest X-ray, systematic laboratory tests, and chest CT, if necessary, every 3 months. Patients with localised disease that had a complete response to chemotherapy received cranial irradiation. Other treatment options were registered (palliative radiotherapy and second line chemotherapy), progression free survival and global survival. Death of a patient caused by small cell lung cancer was the assessment criterion.

Analysis of Neuron-Specific Enolase (NSE)

Venous blood samples were taken in all patients, at the time of diagnosis and after the 4th and 6th course of chemotherapy. These samples were sent directly to the microbiology department. All blood samples were centrifuged and sera were separated. Sera samples

were divided into aliquots and stored at –20°C until the moment of analysis. Commercial SNE micro ELISA (DRG International Inc., Mountainside, NJ, USA) equipment was used, with an automated micro ELISA (ETI-Max 3000; Dia Sorin S.p.A., Saluggia, Italy) analyser, according to manufacturer's instructions. Five different calibration solutions were used, 5-200 μg/l (calibration solution I: 5 μg/l, calibration solution II: 25 μg/l, calibration solution III: 50 μg/l, calibration solution IV: 100 μg/l, calibration solution V: 200 μg/l). Patient's μg/l absorbency values were obtained using the calibration curve method.

Quality control and validation criteria were assessed according to the manufacturers recommendations (DRG International [2007] Instruction Manual: Neuron Specific Enolase ELISA; USA [www.drg-international.com]).

Statistical Analysis

Statistical analyses were carried out using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) program. In this study, categorical variables are presented as frequency tables, and numerical variables are presented in the form of descriptive statistics (mean, standard deviation, medium, minimum and maximum). For the comparison of pre and post treatment values of NSE Wilcoxon's test was used. For the comparison of SNE values between categorical variables in the 2 groups, the Mann-Whitney U test was used and for comparison between categorical variables of more than 2 groups the Kruskal-Wallis test was used. To assess the relationship between numerical data and SNE values Spearman's correlation coefficient was used. A value of $p < 0.05$ was considered statistically significant. In the multivariate analysis model a Cox regression analysis was used with modelling by means of the backward procedure (likelihood ratio, LR).

Results

We included 65 patients in this study. Table 1 shows their general characteristics. A combination of etoposide and cisplatinum was administered to 51 patients (78.5%), and 14 patients (21.5%) received a combination of carboplatinum and etoposide. A total of 4-6 courses of chemotherapy were administered to 56 patients. Before completing the study 7 patients died due to the disease. In 2 patients chemotherapy was interrupted due to treatment related toxicity. Second line chemotherapy was administered to 12 patients, one received third line chemotherapy and one patient underwent endobronchial electrocautery. Average follow-up was 12 months after initial diagnosis. Cranial prophylactic irradiation was applied to 14 patients.

Pre-treatment SNE values in serum were determined in all patients, whereas post treatment values were determined in 47 cases (fig. 1). Pre-treatment values did not present any correlation with age, sex, smoking history (pack year), general condition, progression free survival and global survival. SNE values were significantly higher in patients who died from the disease. Pre-treatment values were significantly lower in patients who responded to treatment (table 2).

No significant correlation was found between post treatment values and response to chemotherapy, progression-free survival, global survival and patient prognosis (table 3). The difference between pre and post treatment values was not significantly related to response to treatment, progression free survival and global survival (table 4).

A Cox regression analysis was performed by modelling using the backward procedure (likelihood ratio, LR). The model used included factors that affected survival such as age, sex, disease stage, ECOG score, pre-treatment SNE serum values and changes in SNE values between the pre-treatment and post treatment period. The most important factor that affected survival was pre-treatment marker value in serum ($p = 0.013$; risk coefficient [RC] = 1.002; 95% confidence interval [CI], 1.001-1.004).

Table 1
Demographic and clinical characteristics of patients with small cell lung cancer

Parameter	Value	%
Age, years, mean ± SD (limits)	60.9 ± 10.7 (38-81)	
Sex (n)		
Males	61	93.8
Females	4	6.2
Tobacco use, pack years, mean ± SD (limits)	47.0 ± 21.6 (10-130)	
ECOG (n)		
1	41	63.1
2	17	26.2
3	6	9.2
4	1	1.5
Stage (n)		
Limited	42	64.6
Disseminated	23	35.4
Location of metastasis (n)		
Liver	14	21.5
Adrenal	4	6.2
Brain	4	6.2
Bone	2	3.1
Abdominal lymph glands	2	3.1
Lung	1	1.5
Pancreas	1	1.5
Response to chemotherapy (n)		
Complete	20	30.8
Partial	28	43.1
Progressive	5	7.7
Without treatment	12	18.5
Progression-free survival, months; mean ± SD (limits)[a]	4.6 ± 2.7 (1-10)	
Prognosis (n)		
Dead	33	50.8
Alive	32	49.2
Survival, months; mean ± SD (limits)	8.6 ± 4.9 (1-21)	
NSE serum values (μg/l); mean ± SD (limits)		
Pre-treatment (n = 65)	125.3 ± 183.3	
Post treatment (n = 47)	26.9 ± 49.9	

SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; NSE: neuron-specific enolase.
[a]Calculated for 32 patients.

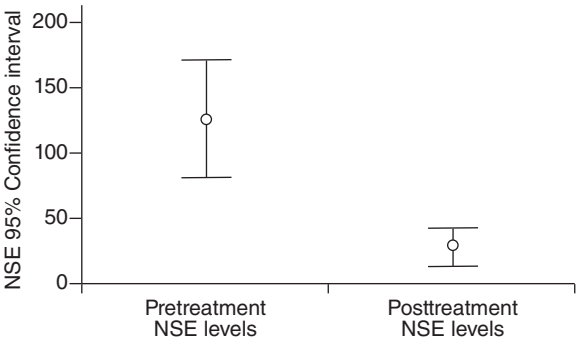

Figure 1. Pre and post treatment serum values of neuron-specific enolase (μg/l). Captions: 1) 95% confidence interval for NSE serum values. 2) Pre-treatment NSE values. 3) Post treatment NSE values.

Discussion

In normal practice, an ideal tumour marker is appropriate for screening and early diagnosis, assessing prognosis and supervising

Table 2
Pre-treatment neuron-specific enolase (NSE) serum values according to the characteristics of the disease and the patients, and response to chemotherapy

Parameter	NSE pre-treatment serum values (μg/l)	r	p
Age, years		−0.208	0.096[a]
Sex (n); mean ± SD (limits)			
Males	130.8 ± 187.8		0.306[b]
Females	41.3 ± 39.7		
Tobacco use, pack years		−0.208	0.096[a]
ECOG, mean ± SD (limits)			
1	103.7 ± 140.4		0.373[c]
2	144.8 ± 208.4		
3	175.2 ± 335.2		
4	380.0		
Stage (n), mean ± SD (limits)			
Limited	126.0 ± 186.6		1.000[b]
Disseminated	124.0 ± 181.2		
Response to chemotherapy; mean ± SD (limits)			
Complete	60.2 ± 95.2		0.007[c]
Partial	125.6 ± 162		
Progressive	349.6 ± 287.3		
Without treatment	139.7 ± 233.7		
Complete-Partial			0.018[d]
Complete-Progressive			0.004[d]
Partial-Progressive			0.020[d]
Progression-free survival, months[b]		−0.289	0.109[a]
Prognosis; mean ± SD (limits)			
Dead	174.4 ± 229.4		0.016[b]
Alive	74.6 ± 99.3		
Survival, months		−0.098	0.439[a]
Mean (n = 65); mean ± SD (limits)	125.3 ± 183.3		

SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; NSE: neuron-specific enolase.
[a]Spearman's Correlation.
[b]Mann-Whitney U test.
[c]Kruskal-Wallis test.
[d]Mann-Whitney *post hoc* U test (value of p = 0.05/6 = 0.0083).

Table 3
Post-treatment neuron-specific enolase (NSE) serum values according to response to chemotherapy and prognosis

Parameter	NSE pre-treatment serum values (μg/l)	r	p
Response to chemotherapy; mean ± SD (limits)			
Complete (n = 20)	22.2 ± 44.9		0.767[b]
Partial (n = 24)	25.3 ± 43.1		
Progressive (n = 3)	71.7 ± 116.3		
Progression-free survival, months		0.142	0.470[a]
Prognosis, mean ± SD (limits)			
Dead (n = 17)	27.2 ± 49.5		0.981[c]
Alive (n = 30)	26.8 ± 51.0		
Survival, months		0.089	0.512[a]
Total (n = 47); mean ± SD (limits)	26.9 ± 49.9		

SD: standard deviation; NSE: neuron-specific enolase.
[a]Spearman's Correlation.
[b]Kruskal-Wallis test.
[c]Mann-Whitney U test.

the effects of treatment and during follow-up. SNE is one of the tumour markers most commonly used in patients with small cell lung cancer. SNE values in serum are high in almost 75% of patients with this tumour at the time of initial diagnosis.[11,12] In spite of the high frequency of an increase of NSE values in patients with this disease, data is not conclusive in relation to its predictive value for disease extension.[13,14] correlation with clinical response[15,16] distinction between complete and partial response,[14,17] prediction of relapses[15,16] and correlation with survival.[13,16]

In general, it has been seen that low values of this marker are associated with a complete response and prolonged survival in patients who undergo chemotherapy.[5] In this study, pre-treatment serum values of SNE were significantly lower in patients with a satisfactory response to chemotherapy. SNE serum values were significantly lower in those patients with a complete response in comparison with those with a partial response as well as in those with a partial response in comparison with those with disease progression. Post treatment serum values were not associated with response to chemotherapy.

The relation between serum values of SNE and presence of metastatic disease has also been investigated. Quoix et al.[13] described that SNE values were significantly higher in patients with disseminated disease in comparison with those with limited disease. Furthermore, they suggested that the predictive value of this marker was greater if it was assessed simultaneously with lactate dehydrogenase concentrations. Van de Pol et al.[11] found that the

Table 4
Changes in serum values of neuron-specific enolase (NSE) between pre and post-treatment interval according to response to chemotherapy

Parameter	NSE change in serum values (μg/l)	r	P
Response to chemotherapy; mean ± SD (limits)			0.111 [b]
Complete (n = 20)	−45.3 ± 41.3		
Partial (n = 24)	−68.0 ± 32.8		
Progressive (n = 3)	−39.1 ± 103.8		
Progression-free survival, months		0.315	0.103 [a]
Survival, months		0.091	0.542 [a]
Total (n = 47); mean ± SD (limits)	−56.5 ± 43.0		

SD: standard deviation; NSE: neuron-specific enolase.
[a]Spearman's Correlation.
[b]Kruskal-Wallis test.

values of this marker were not significantly different according to presence of metastatic disease or location of extrathoracic metastasis. The results of this study showed that SNE serum values were not significantly different between patients with disseminated and limited disease.

It has been documented the SNE is an independent prognostic factor for survival in small cell lung cancer.[3] Bonner et al.[18] reported that pre treatment values and treatment induced minimum values were prognostic variables independent of time to progression and survival in patients with this cancer. Pre-treatment values of this marker had an inverse correlation with time to progression and survival in patients with this disease. Post treatment serum values were not associated with response to chemotherapy, progression-free survival, global survival and patient prognosis. Furthermore, the differences between pre and post treatment values were not related to response to chemotherapy, progression free survival and global survival.

SNE serum values are not a useful tumour marker to predict relapses.[19] Wójcik et al.[20] described a significant relationship between disease free survival and initial values in patients with small cell lung cancer. It has been reported that follow-up of these values in these patients is a satisfactory prognostic variable for tumour activity; however, the values do not predict the locations of metastatic lesions.[11] In this study, serum values determined during pre and post treatment periods are not related to progression free survival.

It has been noted that different markers are associated with prognosis in small cell lung cancer. One of these, the ERBB2 oncogene, is associated with the presence of disseminated disease.[21] In patients with small cell lung cancer serum values of NSE are usually high. This is why many studies have been carried out on disease extension, response to chemotherapy, relapses, progression free survival, and global survival.[11,12] In contrast to other studies, we have determined pre and post treatment serum values to predict prognosis in patients with this disease. However, this study has some limitations. Firstly, it was an open study. This may have resulted in bias during data analysis. Secondly, it included a small sample of patients with different stages of the disease. Pre-treatment values did not present any correlation with age, sex, smoking history, extension of the disease, general condition, progression free survival and global survival. However, low pre-treatment values have been related with a satisfactory response to chemotherapy. Similarly, post treatment values and the magnitude of the change between pre-treatment and post treatment values did not have a significant correlation with response to chemotherapy, progression free survival and global survival.

Conclusions

Patients with small cell lung cancer are a complex problem due to the difficulty in obtaining a satisfactory response to treatment. Additional research is necessary to help select patients for chemotherapy and other additional treatment options. In this prospective, open study, we compared pre and post treatment NSE values in patients with disease that underwent chemotherapy. We concluded that SNE serum values are not related to the stage of disease, however, low serum values prior to treatment could be useful to predict a satisfactory response to chemotherapy.

Contributions of the Authors

AEE carried out the molecular genetics studies, participated in sequence alignment and wrote the paper. AG carried out the immunoassay. FT participated in sequence alignment. AEE and OB participated in the study design and carried out the statistical analysis. ZZU and SZG conceived the study, participated in its design and coordination, and helped to write the paper. All the authors read and approved the final paper.

Conflict of Interest

The authors state that they have no conflicts of interest.

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