Pretreatment Inflammatory Indexes are Associated with Response to First-Line Platinum-Based Chemotherapy and Prognosis of Small Cell Lung Cancer Patients

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ABSTRACT

The immune system plays an important role in the progression of the cancer. Some studies have shown that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are prognostic indicators in many cancers. In this study we investigated the whether NLR and PLR predicts survival of small cell lung cancer (SCLC). 177 SCLC patients treated with Cisplatin + Etoposide chemotherapy were admitted to the study. After third cycle of chemotherapy the response was evaluated clinically and radiologically and randomized into 2 groups based on responses to chemotherapy; Progressive disease group (PD) or Response group (Complete Response+ Partial response+ Stable Disease). A NLR ≥ 5 was considered high. There was no difference between the two groups in terms of the initial NLR; however control NLR values were different. NLR values were significantly decreased after chemotherapy for both groups when compared to baseline values in determining intra-group analyzing (for PD group p= 0.05; for Response group p= 0.013). NLR value < 5 patient group had longer overall survival than NLR ≥ 5 patient group (10 vs. 7 months; p= 0.015). Age. NLR. smoking. ECOG PS 2 and stage were independent prognostic factor for overall survival (OS) (respectively; p< 0.001. p= 0.006. p= 0.05. p= 0.02. p= 0.03). but PLR was not independent prognostic factor for OS. In this study. we evaluated the relationship between NLR and SCLC. and found that NLR is a potential prognostic serum marker in patients with SCLC. Also current smoking. aging. poor performance status and extensive disease are prognostic factors in SCLC patients.

Keywords: Small cell lung cancer, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Prognosis

ÖZET

Tedavi Öncesi İnflamatuar İndeksler İle Birinci Basamak Platin Temelli Kemoterapi Yanıtı Ve Küçük Hücreli Akciğer Kanseri Hastaların Pronozu Arasındaki İlişki

İmmun sistem kanser hastalığının progresyonunda önemli rol oynar. Bazı çalışmalar nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranının (PLO) birçok kanserde prognostik göstergeler olduğunu göstermiştir. Bu çalışmada NLO ve PLO'nun platin bazlı kemoterapi ile tedavi edilen küçük hücreli akciğer kanserinin (KHAK) sağkalımını tahmin edip etmediğini araştırdık. KHAK tanısı ile sisplatin + etoposid kemoterapisi alan 177 hasta çalışmaya alındı. Kemoterapiye verilen yanıtlara göre; Progresif hastalık grubu (PD) veya yanıtlı grup (Komple Yanıt + Kısmi yanıt + Stabil Hastalık) şeklinde 2 gruba randomize edildi. ≥ 5 NLO değeri yüksek olarak kabul edildi. Başlangıç NLO açısından iki grup arasında fark yoktu. Ancak kontrol NLO değerleri gruplar arasında farklıydı. Kemoterapi sonrası NLO değerleri başlangıç değerleri ile karşılaştırıldığında her iki grupta da anlamlı olarak azaldı (PD grubu p= 0.05; Yanıtlı grub p= 0.013). NLO değeri < 5 olan hasta grubunun NLO değeri ≥ 5 hasta grubuna göre genel sağkalım süreleri uzundu (10'a karşı 7 ay; p= 0.015).

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Yaş. NLO. sigara içimi. ECOG PS 2 ve evre genel sağkalım (GS) için bağımsız prognostik faktör olarak belirlendi (p değerleri sırasıyla; p< 0.001. p= 0.006. p= 0.05. p= 0.02. p= 0.03). Fakat PLO. GS için bağımsız prognostik bir faktör olarak tespit edilmedi. Bu çalışmada NLO ve SCLC arasındaki ilişkiyi değerlendirdik ve NLO'nun SCLC'li hastalarda potansiyel prognostik serum belirleyicisi olduğunu tespit ettik (p= 0.006). Ayrıca aktif sigara içiciliği (p= 0.05). ileri yaş (p< 0.001). düşük performans (p= 0.02) ve yaygın hastalık durumunun (p= 0.03) SCLC hastalarında prognostik faktörler olarak saptadık.

Anahtar Kelimeler: Küçük hücreli akciğer kanseri, Nötrofil-lenfosit oranı, Trombosit-lenfosit oranı, Prognoz

INTRODUCTION

Small cell lung cancer (SCLC) is composed of approximately 20% of all lung malignancies. SCLC is represented by early dissemination. a quick doubling time. and elevated sensitivity to chemotherapy and radiotherapy.[1.2] According to an important guide. the stages of SCLC are classified as extensive disease (ED) or limited disease (LD).[3] Despite about one third of patients with SCLCcategorized as LD at the time of diagnosis. they also have a poor prognosis.[4]

Generally. inflammatory cells around the tumor microenvironment are considered to have important effects on tumor development.[5] The systemic inflammatory response feature alters the proportional levels of circulating leukocytes; the well-known neutrophilia is concomitantly a relative lymphocytopenia.[6] Evaluation of the inflammatory response to the neoplasm may be easier and more cost-effective in clinical practice. Recently. the effects of the immune system on cancer progression have been investigated. and at the time of the diagnostic. hematological markers including neutrophil. lymphocyte levels. and neutrophil lymphocyte ratio (NLR) were anticipated as prognostic tools in diverse malignancies.[7-9]

Previous research uncovered that a high pretreatment NLR was in relation to reduce survival in cancer patients.[8-10] The Japan Multinational Trial Organization and The European Lung Cancer Working Group discovered that a high neutrophil level was an independent risk factor for worse outcome in patients with non-small cell lung cancer.[11.12] Parallel results can be found in another study.[13] However. there has been a limited amount of research that has appraised the association between NLR. platelet lymphocyte ratio (PLR). and mortality in small cell lung cancer patients.[14.15] The aim of this research was to explore the correlation between inflammatory markers (NLR and PLR). therapy response.and overall survival in SCLC patients. who received first-line platinum-based chemotherapy.

PATIENTS AND METHODS

One hundred and seventy-seven consecutive SCLC patients were diagnosed between April 2004 and March 2011 were retrospectively reviewed.The study was approved by the Regional Scientific Ethical Committee (2018/386). The baseline staging work-up included a complete history. complete bloods counts. and computed tomography (CT) of the thorax and abdomen. Tumor stage was defined according to the International Association for the Study of Lung Cancer. IASLC. issued consensus report.[16] This report suggested that local extension to regional lymph nodes. including contralateral. mediastinal. and contralateral supraclavicular should be considered aslimited disease (LD). All patients were examined at the discretion of the treating oncologist. before and after three cycles of chemotherapy with CT scan. whole blood test. and LDH. Potential prognostic factors that were analyzed included gender (male vs. female). ECOG PS (The eastern cooperative oncology group;PS. performance status). staging.smoking history. hematological parameters (neutrophil. lymphocyte). and biochemical parameters (LDH. albumin. protein).Patients were excluded. who might affect the rate of NLR. in the cases of active infection. G-CSF therapy. chronic glucocorticoid use or PS> 2. Retrospective analysis was performed regarding the best response to chemotherapy. and survival. An Abbott Architect C16000 instrument was used for LDH. albumin. and protein studies. The cut off value for LDH below normal upper limit (ULN)< 220 U/L was accepted. NLR was defined as the absolute neutrophil count divided by the absolute

Table 1. Patients characteristics

Demographics	n	%
Medianage	56 (36-80) yrs	
Gender		
Male	161	91
Female	16	9
Symptoms		
Cough	39	22
Shortness of breath	63	35.6
Backache	22	12.4
Chest pain	12	6.8
Hoarseness	11	6.2
Other	30	16.9
Duration of symptoms		
≥ 3 months	67	37.9
< 3 months	110	62.1
ECOG PS		
0	85	48
1	77	43.5
2	15	8.5
Stage		
Limited disease	72	40.7
Extensive diseases	105	59.3
Smoking history		
Current	59	33.3
Former	118	66.7
Metastatic site		
Liver	21	11.8
Lung	6	3.4
Bone	14	7.9
Brain	10	5.8
Adrenal gland	6	3.4
LIver and bone	16	9.0
Multiple	32	18.0
No metastases	72	40.7

lymphocyte count. An NLR of 5 or greater was considered elevated in accordance with an earlier report and the median value of NLR (median NLR: 5).[17] PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. The PLR median value was found to be 180. The cut-off value was determined to be 180 and over. After a third cycle of chemotherapy. response was reevaluated clinically and radiologically by using a CT scan of the thorax and abdomen according to Recist criteria (EORTC version 2000).[18] Patients were classified into two groups according to their chemotherapy response; Progressive disease (PD) group vs. Response group (complete response: CR+ partial response: PR + stable disease: SD).

Table 2. Hematological and biochemical parameters

	Median
NLR	5.00 (0.33-34)
PLR	180 (24.31-1082)
HB	13 (9.2-17.9) g/dL
PLT	309 (110-746)10^3/uL
ALB	3.6 (1.2-6.9) g/dL
GLOB	6.9 (4.5-9) g/dL
Alb/Glob	0.52 (0.20-0.97)
LDH	282 (116-4445) U/L

Statistical Analysis

All analyses were performed with SPSS 18 software package program. The duration of OS was calculated from date of pathologic diagnosis and death due to any cause or until the date of the last follow-up visit for patients still alive. The OS 95% confidence intervals (CI) were calculated with the Kaplan–Meier method. Curves were compared using the log-rank test. Univariate and multivariable survival analysis was performed using Cox regression performed to assess for patient characteristics and NLR. Factors with a prognostic association in the univariate analysis were entered into a multivariate Cox regression model. The Wilcoxon Signed Ranks test was used for intra-group analysis and the Mann-Whitney U test was used for inter-group analysis. P values of < 0.05 were considered significant.

Table 3. Comparison of NLR between two groups

Groups	PD (n= 59)	CR+PR+SD (n= 118)	p
Baseline NLR	3.91 (2.51-6.16)	3.13 (2.06-5.20)	0.17
Control NLR	2.55 (1.15-5.96)	1.60 (0.58-4.85)	0.03
p	0.05	0.013	

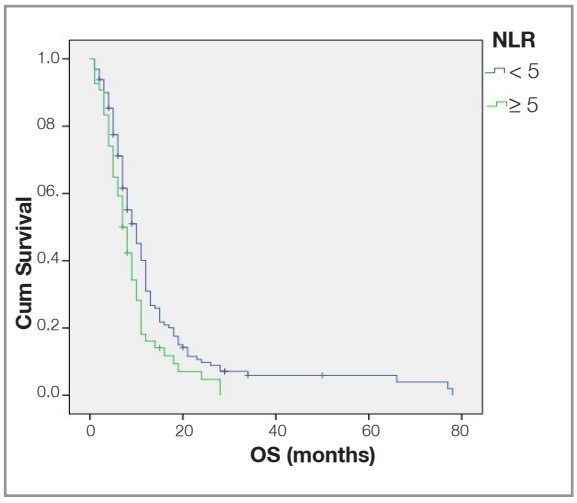

Figure 1. NLR < 5 patients had longer OS compared to NLR ≥ 5 in Kaplan-Meier analysis (10 months vs. 7 months; log rank p= 0.015)

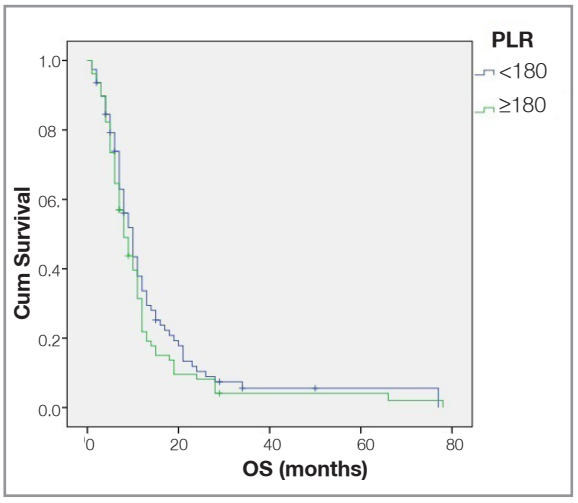

Figure 2. PLR< 180 patients did not have longer OS compared to PLR ≥ 180 in Kaplan-Meier analysis (10 months vs. 8 months; log rank p= 0.26)

RESULTS

In this study. 177 small cell lung carcinoma patients. who were diagnosed pathologically and treated with cisplatin + etoposide chemotherapy were included. After three cycles of therapy. 59 (33.3%) patients had progressive disease (PD). 53 (29.9%) patients had stable disease (SD). 58 (32.8%) patients had partial response (PR). and 7 (4%) patients had complete response (CR). Demographic characteristics of the patients are shown in Table 1. Hematological and biochemical data of the patients are shown in Table 2. There was no difference between the two groups in terms of the initial NLR. However. control NLR values were different (Table 3). NLR values were significantly decreased after chemotherapy for both groups. when compared to baseline values in determining intra-group analyzing (PD group p= 0.05; CR + PR + SD group p= 0.013).When the NLR values were compared according to the staging at the time of diagnosis (limited or extensive diseases). the median NLR rate was 3.09 (2.24 to 3.09) for limited disease and 3.70 (2.49 to 6.00) for extensive disease. but the difference was not significant (p= 0.154).There was no differences between extensive and limited disease according to NLR< 5 respectively (54.9% and 45.1%; p= 0.15).When the patients were randomized according to the proportion of the NLR at time of diagnosis; "≥ 5 or < 5". NLR < 5 patients had longer OS compared to NLR ≥ 5 in Kaplan Meier analysis (10 months (95% CI 8-11) vs. 7 months (95% CI 6-9); log rank p=0.015) (Figure-1). OS was 10 months (95% CI 8-11) in PLR <180 and 8 months (95% CI 6-9) in PLR≥ 180 (log rank p= 0.26. Figure 2). Furthermore. cox regression analysis showed no effect of PLR on mortality.

PS. stage of diagnosis. smoking. age. LDH. and NLR were found to be important factors for mortality in univariate analysis (Table 4). However.in multivariate analysis ECOG PS 2 patients had a higher risk of mortality than PS 0 patients. Also. extensive disease. increase in NLR. continuing to smoke. and advanced age were found to be higher mortality factors (Table 5).

DISCUSSION

The knowledge of prognostic factors therefore. is substantial. so that it permits classifying patients who are aspirants for appropriate treatment. Performance status. weight loss. and a two-stage system have been the main prognostic tools in SCLC patients.[19] Although some discussions continue. other prognostic factors. such as gender and age. are well known as prognostic tools for SCLC.[20]

Table 4. Univariate cox regression analyze for mortality

	HR	95% CI	p
SEX	1.007	0.569-1.785	0.980
AGE	1.033	1.015-1.052	<0.001
PS 0		0.036	
PS1	1.271	0.898-1.800	0.176
PS2	2.141	1.174-3.904	0.013
STAGE	1.52	1.08-2.145	0.016
SMOKING	1.452	1.016-2.075	0.04
NLR	1.065	1.027-1.105	0.001
LDH	1.000	1.000-1.001	0.011
GLOBULIN	1.018	0.983-1.054	0.329
ALBUMIN	1.003	920-1.095	0.92
ALB/GLOB	0.586	0.11-3.124	0.532
PLR	1.000	0.999-1.001	0.583
PLATELET	1.000	1.000-1.000	0.581

High amounts of serum LDH have been hypothesized to represent the existence of a hypoxic environment relation to cancer cells. Correspondingly. the oxygenation condition of a neoplasm has been indicated to be a substantial determinant of clinical effectiveness of radiotherapy and chemotherapy.[19] Serum LDH was one of the most important prognostic variables in colorectal cancer and lung cancer.[22.23] Although LDH was found to be significant with univariate analysis in our study. however it was not statistically significant in multivariate analysis.

There is a requirement for easily accessible tests for better prognostic and predictive systems in cancers. especially in SCLC. Elevated neutrophil levels have been correlated with adverse outcome in patients with diverse types of malignancy and although the mechanism is not wholly understood. a multifactorial process has been assumed.[24.25] The first hypothesis is that neutrophils may restrict the immune system. Tumor-associated neutrophils also support the remodeling of the extracellular matrix by enzymatic effects. It has been demonstrated that neutrophil-derived oncostatin M signals human breast malignant cells to secret VEGF and increases aggressiveness.[26] A low lymphocyte count however. has been linked with worse outcomes in patients with cancer attributed to immu-

Table 5. Multivariate cox regression analyze for mortality

	HR	95% CI	p
ECOG PS0			0.05
ECOGPS1	1.227	0.860-1.750	0.25
ECOGPS2	2.032	1.091-3.784	0.025
Stage	1.478	1.035-2.112	0.032
Smoking	1.402	0.970-2.025	0.05
NLR	1.055	1.016-1.097	0.006
Age	1.036	1.017-1.056	< 0.001

nity. with destruction of host tumor cells.[27] NLR can be interpreted as the equilibrium between a pro-tumor inflammatory situation and anti-tumor immune situation. Patients with a high NLR have relative lymphocytopenia and neutrophil leukocytosis. which points out that the equilibrium is lost in favor of a pro-tumor inflammatory status and is linked with a worse oncologic outcome.[28.29]

In lung malignancy. two previous investigations have explored the correlation between NLR and outcome. In a retrospective review of patients. who had undergone definitive operation for NSCLC. found that an elevated NLR on preoperative blood tests was correlated with a higher stage and an increasing NLR is an independent risk factor.[8] Another study investigated the role of pretreatment NLR amount on the survival in chemonaive patients with stage IIIB-IV NSCLC. They suggested that the pretreatment neutrophil amount was linked with reduced OS and PFS.[11] In our study. the LD and ED groups were similar in terms of NLR when the patients were classified for staging at the time of diagnosis. An increase in NLR values was found to boost the risk of mortality 1.05-fold in multivariate analysis. Similarly. patients with an NLR< 5 had longer survival than those with ≥ 5 ones. These results are similar to previous observations on the relationship between NLR and lung cancer and prove our hypothesis and propose that an elevated NLR is an independent predictor for worse survival in patients with SCLC.[8.11]

The correlation between NLR and clinical response to therapy was previously detected in different cancers. These investigations all showed that an enhanced pretreatment NLR was a predictive tool for poor therapy response.[30.31] In our study. when comparing the PD group and response (CR + PR + SD) group. they did not differ in terms of NLR at the time of diagnosis. However. both groups showed a significant decrease in rates of NLR due to the effect of chemotherapy. Lower values were found in the response group than in the PD group after three cycles of chemotherapy. Our investigation also demonstrated that decreased post-treatment NLR was an independent factor for predicting a good response to first-line platinum-based chemotherapy.

Previous studies have identified the prognostic role of PLR in many malignant tumors. including pancreatic adenocarcinoma. breast cancer. ovarian cancer. and NSCLC. but not SCLC.[32.33] Unlike literature. our study did not demonstrate the effect of PLR on survival in the cox regression analysis and Kaplan Meier analysis.

Tobacco contains seventy chemicals. which are known carcinogens.[34] Exposure to tobacco smoke initiates a mutagenesis effect in the occurrence of lung cancer. and sustained smoking explains recurrence in early stage lung cancer and increased mortality.[35] In a study that illustrated that nicotine was able to activate STAT3 in human macrophages. it was proposed that the formation of pre-metastatic regions and metastases in patients with smoking-linked NSCLC might be sensitive to a STAT3 blockade.[36] In the present study.mortality was increased 1.4-fold in active smokers during a chemotherapy course and this is confirmed in general literature.

Aging is linked to a number of age-related physiologic alterations. which elevate the risk of toxicity related to chemotherapy.[37] Bone marrow reserves. liver. and renal functions reduce with age and these alterations could change drug pharmacokinetics and have an influence on the toleration of systemic cytotoxic chemotherapy.[38] Moreover. aging is correlated with a significant frequency of comorbidity and the presence of geriatric syndromes. which are significant in a patients' prognosis.[39] Depending on the possible causes previously mentioned. mortality risk was 1.03-fold increased with increased age in our study.

ECOG PS has been shown as a prognostic element for outcome with first and second line treatment of patients with NSCLC.[40.41] Previously treated NSCLC patients with worse ECOG PS are detected to have reduced survival.[42] In the present study. ECOG PS was found to be an important prognosticelement for mortality (mortality risk was 2-fold increase in the PS2 patients than in the PS0 patients).

In this study. the ED group patients had a 1.47-fold mortality risk than the LD group patients at the time of diagnosis. Generally.SCLC is considered a systemic disorder and survival is worse. even in patients with LD.[43] Extensive disease continues to have a worse prognosis as no considerable improvement has appeared in systemic chemotherapeutic drugs or molecular targeted agents. Although ED has a good sensitivity to chemotherapy in a first-line setting. there is no effective chemotherapeutic drug in second line treatment to provide a meaningful response and improved outcome. As opposed to NSCLC. rapid increase in tumor and worsening in patient performance status restricts the ability to use second-line therapy and leads to overall poor outcome and lack of progress in SCLC patients.[44]

Consequently. pre-treatment NLR was clarified as a considerable prognostic tool of SCLC. together with other well-known factors. such as stage. age. smoking history. and performance status. and could be tools for response to chemotherapy and prognosis. Despite these findings. the clinical benefit of NLR and PLR should be confirmed by prospective analysis.

The main limitation of this research is that the sample was relatively small. non-randomized. retrospective. and came from a our single- center. which might cause the generalization of the results. In addition. we could not evaluate all of the factors that would affect NLR and PLR results.

CONCLUSION

In this study. we demonstrated that NLR is a potential prognostic serum marker than PLR in patients with SCLC. Current smoking. aging. poor performance status. and extensive disease are also prognostic factors in SCLC patients.However. the prognostic significance of NLR and PLR should be investigated in a large randomized prospective clinical trial.

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