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ORIGINAL ARTICLE

Prognostic importance of the nutritional status and systemic inflammatory response in non-small cell lung cancer

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Summary

Purpose: *Despite all primary prevention and therapeutic efforts around the world, non-small cell lung cancer (NSCLC) continues to be an important public health problem. In the treatment of patients, laboratory parameters can be used for the determination of treatment intensity. These laboratory parameters should be easily accessible, cheap and easy to use. For this purpose, the prognostic importance in NSCLC of serum albumin levels, neutrophil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (TLR) was investigated in the present study.*

Methods: *Serum albumin levels and body mass index (BMI) were used to determine the nutritional status and NLR and TLR were used to determine the systemic inflammatory response (SIR).*

Results: *While median survival was 9.1 months in hypoalbuminemic patients, it was 16.4 months in normoalbuminemic patients (p=0.002). The relationship of positive or negative NLR as an indicator of SIR with median survival was statistically significant (p=0.006). While median survival was 7.8 months for patients with NLR ≥5, it was 14.7 for the patients with NLR <5 (p=0.006). TLR as a SIR indicator was not connected with median survival (p=0.072).*

Conclusion: *Serum albumin, indicating the nutritional status and the NLR as an indicator of SIR, are significantly related with prognosis in locally advanced and metastatic NSCLC. Serum albumin measurement and calculation of NLR are easily accessible, cheap and easy to use laboratory methods. We consider that serum albumin levels and NLR can be utilized in the treatment planning of NSCLC patients.*

Key words: *inflammatory response, lung cancer, non-small cell lung cancer, nutritional status*

Introduction

Lung cancer is the most common cause of death from cancer. Lung cancer is divided in two basic histological types: small cell lung cancer (SCLC) and NSCLC. NSCLC forms 80-85% of all lung cancer cases [1]. In NSCLC, comorbid diseases, performance status, stage of disease and smoking habits are known prognostic factors.

In cancer patients, malnutrition-related morbidity ranges between 40-80% [2,3]. Today, there is evidence showing that existence of SIR is associated with increasing weight loss, increase in resting energy expenditure, fat-free tissue loss and functional fall [4]. Malnutrition is related with longer hospitalization, complications and mortality. Hypoalbuminemia and malnutrition are correlated and are frequently encountered in NSCLC [5]. While examining the nutritional status of cancer patients, besides clinical parameters as Subjective Global Assessment (SGA) and proportion of loss in fat-free mass, serum albumin levels and SIR indicators can be used as well [3,6].

NLR, TLR, and C-reactive protein (CRP) are indicators of SIR [7]. NLR and TLR have shown to be prognostic factors in many cancer types [8,9]. It has been shown that CRP, which is a non-specific indicator of inflammation, is associated with bad prognosis in NSCLC [10,11]. The prognostic

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Table 1. Lab parameters assessed in this study

Parameters	*Mean±standard deviation*	*Median*	*Range*
Age (years)	59.3±11.51	59	30-88
AST (U/L)	24.5±15.6	19	8-228
ALT (U/L)	23.4±16.7	19	5-90
LDH (U/L)	226.3±86.4	203	100-673
Hb (g/dl)	11.4±2.3	11.7	4.1-15.2
Neutrophils ($10^3/mm^3$)	6.81±3.6	6.0	2.24-28.3
Lymphocytes ($10^3/mm^3$)	1.93±0.96	1.79	0.16
Platelets ($10^3/mm^3$)	347.7±139.7	321	131-986
Albumin	3.7±0.7	3.85	2.0-4.8
Height (cm)	164.6±8.2	165.5	145-182
Weight (kg)	65.2±12.9	65	40-100
BMI (kg/m^2)	24.1±4.9	23.3	14.7-39

importance in NSCLC of another inflammatory response indicator, namely the pre-treatment neutrophil count or NLR has been investigated by many authors [12].

In this study, serum albumin level and BMI were used for the determination of the nutritional status, and NLR and TLR were used for the determination of SIR and its prognostic significance during treatment of NSCLC patients.

Methods

Patients with histologically confirmed NSCLC at the Medical Oncology Clinic of Antalya Training and Research Hospital between 2008-2010 were included in the study. Patients whose initial evaluation was made at another center and were treated in our clinic were excluded from the study. Disease stage and treatments applied were retrieved from the patient records. Prior to chemotherapy, complete blood count and serum biochemistry including liver (AST, ALT, total protein, albumin) and renal (BUN, creatinine) function tests were registered. Serum albumin level as biochemical indicator of the nutritional status was estimated by the bromcresol purple method and values < 3.5 mg/dL were characterized as hypoalbuminemia. NLR was obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. TLR was obtained by dividing the absolute thrombocyte count by the absolute lymphocyte count. Cases with NLR ≥5 and TLR ≥150 were considered to have SIR.

For the clinical evaluation of nutritional status, BMI was used. BMI was calculated as mass (kg) / square of height (m^2). While patients with BMI< 20 kg/m^2 were considered underweight, values of BMI< 18.5 kg/m^2 were accepted as malnutrition.

Statistics

Statistical analysis was performed using SPSS 15.0 software. Utilizing Kaplan-Meier survival analysis, the relationship of survival with the BMI, hypoalbuminemia, NLR, and TLR values were investigated. Statistical differences were confirmed by the log-rank test. Statistical significance was set at $p<0.05$.

Results

A total of 95 patients, of which 18 (18.9%) were female and 77 (81.1%) male, were included in the study. The mean patient age was 59 ± 11.5 years (Table 1). Thirty-one patients (32.6%) had stage IIIA, 17 (17.9%) stage IIIB and 47 (49.5%) stage IV disease. In metastatic patients the most frequently encountered location of metastasis was bone (20 patients; 21.1%), followed by brain metastasis (6 patients, 6.3%) and liver metastasis (5 patients; 5.3%). First-line chemotherapy was docetaxel-cisplatin (25 patients; 26.3%), gemcitabine-cisplatin (34 patients; 35.8%), cisplatin-etoposide (11 patients; 11.6%), paclitaxel-cisplatin (10 patients; 10.6%) navelbine-cisplatin (3 patients; 3.1%), while 8 patients (8.4%) had best supportive care without chemotherapy.

The mean BMI of the patients was 24.1±4.9 kg/m^2. While 7 patients (7.4%) were evaluated as cachectic, 46 patients (48.4%) had normal weight, 22 (23.2%) were overweight and 20 (21.1%) were obese. Concerning albumin levels, 69 (72.6%) patients were normoalbuminemic and 26 (27.4%) hypoalbuminemic. As regards SIR, in 27 patients (28.4%) NLR was ≥5, and in 61 patients (64.2%) TLR was ≥150.

The patients were followed up for 14 months with a mean duration of 14±10.8 months. Mean survival was 19.7 months (95% confidence interval 15.2-24.2). No statistically significant relationship was found between BMI and survival time. There was a statistically significant correlation between the serum albumin levels and survival time ($p=0.002$). While median survival was 9.1 months (95% CI 0.58-17.81) in hypoalbuminemic patients, it was 16.4 months (95% CI 8.52-24.39) in normoalbuminemic patients ($p=0.002$; Figure 1). NLR as an indicator of SIR was strongly related with median survival ($p=0.006$) as the median survival was 7.8 months for patients with NLR ≥5 and 14.7 for patients with NLR <5 (Figure 2). No statistically significant relationship was determined between TLR, another indicator of SIR, and median survival ($p=0.07$). While median survival was 11.2 months for patients with TLR ≥150, it was 17

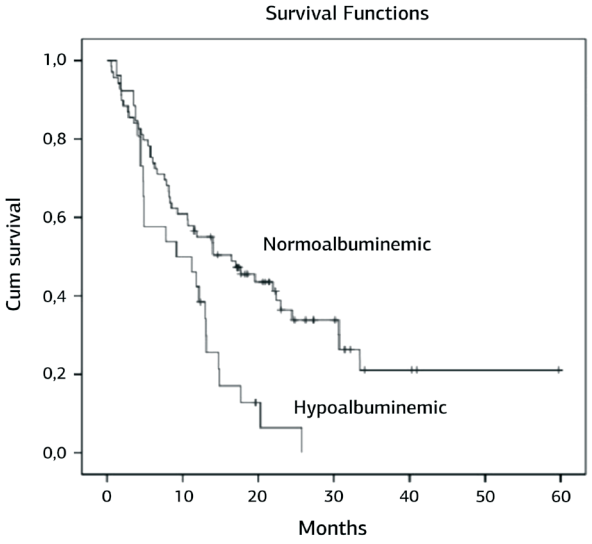

Figure 1. Overall survival for hypo and normoalbuminemic patients (p=0.002).

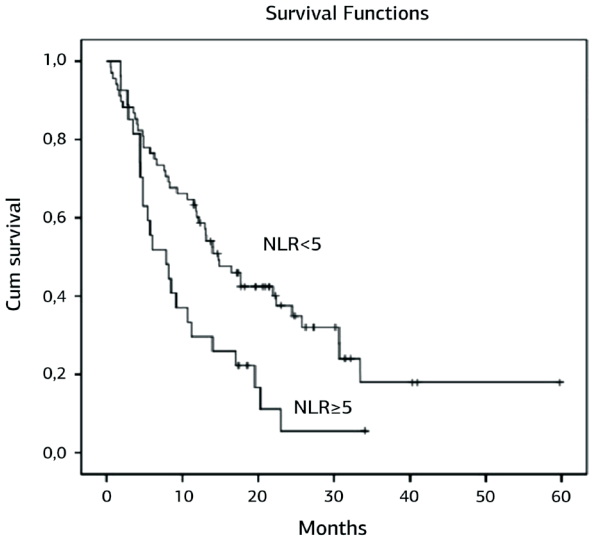

Figure 2. Overall survival in relation with neutrophil-to-lymphocyte ratio (NLR≥5 vs <5; p=0.006).

months for patients with TLR <150 (p=0.072).

Discussion

In NSCLC patients, a statistically significant correlation in terms of median survival was found between the albumin levels, which are an indicator of the nutritional status and NLR, which is an indicator of SIR. The relationship between TLR, which is another indicator of SIR, and median survival time, was not statistically significant. Deterioration in nutritional status is considered as part of the disease and of the treatment in most of the cancer patients. Malnutrition and hypoalbuminemia have been reported in many NSCLC patients [13]. In our study, we showed that survival was shorter in hypoalbuminemic patients.

Jann-Yuan Wang et al., in their study examining prognostic factors in 31 patients who had developed severe radiation pneumonia, have shown that the radiation pneumonia extending out of the radiotherapy field and albumin level < 3.5g/L were associated with short survival [14]. In a study where the prognostic importance of plasma IGF-1 was examined in 77 metastatic NSCLC patients, it has been fixed that IGF-1 level was lower in patients older than 77 years of age and with squamous histology and that IGF-1 levels were correlated with albumin and CRP values. In that study, it was determined that the serum albumin values were related with progression free survival and overall survival [15]. Hypoalbuminemia, in addition to its relation with shorter survival, causes more side effects in patients undergoing chemotherapy [16]. The effect of the nutritional status on surgical treatment outcomes has also been investigated and the results showed no significant correlation between surgical outcomes and nutrional status [17].

It has been shown that deteriorated nutritional status and hypoalbuminemia are related with the SIR parameters [17,18]. Activation of SIR is an important cause of the deterioration of nutritional status [19]. SIR is related with bad prognosis in many solid tumors, particularly in lung cancer, and although the reasons for SIR development in cancer patients are not exactly known, tumor necrosis-related hypoxia, neuroendocrine metabolism alterations, interleukin synthesis and acute phase protein production are incriminated [3]. NLR and TLR, which were used in our study, are commonly used indicators of SIR [20]. NLR has been shown to be bad prognosticator in lung, gastric, pancreatic, ovarian, and colorectal cancers and in liver metastases of colorectal cancer [21-24]. Besides the prognostic role of NLR in cancer patients, it has a role in predicting response to treatment. Although the prognostic role of TLR in ovarian and pancreatic carcinomas has been confirmed [25-27], we were not able to establish such a role for NSCLC patients in our study.

In a study with resected NSCLC patients high NLR value was connected with worse survival. NLR is a prognostic factor not only in early-stage disease but also in locally advanced and metastatic stages [28]. Teramukai et al. have shown that NLR was an independent prognostic factor in stages IIIB and IV NSCLC patients using current chemotherapy regimens, similar to our study [29].

The serum albumin levels indicating the nutritional status and the NLR as an indicator of SIR

are related with prognosis in locally advanced and metastatic NSCLC. Serum albumin measurement and assessment of NLR from whole blood count are easily accessible, cheap and easy to use laboratory methods. We consider that serum albumin value and NLR can be utilized in the treatment planning of NSCLC patients.

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