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RESEARCH

EFFECT OF PROGNOSTIC FACTORS ON SURVIVAL IN ELDERLY PATIENTS WITH NON-SMALL CELL LUNG CANCER

ABSTRACT

Introduction: More than half of newly diagnosed non-small cell lung cancer cases are patients aged more than 65 years and therefore, it is an important health problem in elderly population. In this study, we aimed to investigate effect of various the prognostic factors on survival in non-small cell lung cancer patients aged more than 65 years.

Materials and Method: Ninety-seven non-small cell lung cancer patients aged ≥65 years were included in this study. Performance status was assessed as Eastern Cooperative Oncology Group 0-1 and 2-3. Lower than 12.0 (x 10^9/L) or higher than the value of white blood cell count were classified as normal or higher, respectively. Similarly, lower than 400 (x 109/L) or higher than the value of platelet count were classified as normal or higher, respectively. Mortality risk was analyzed using the multivariate Cox regression model including all the significant variables in the univariate analysis.

Results: Overall survival estimated by Kaplan–Meier test was 11.2 [95% confidence interval (7.55-14.85)] months. In univariate analysis, performance status, stage, white blood cell and platelet counts significantly affected overall survival (p <0.001, 0.001, 0.044, and 0.006, respectively). In multivariate analysis, performance status and platelet count significantly affected overall survival (p <0.001and 0.017, respectively).

Conclusion: Survival in elderly patients with non-small cell lung cancer is significantly influenced by performance status, stage, white blood cell and platelet count. In this patient group, not only age but also these factors should be kept in mind in the treatment planning of the patients.

Key Words: Carcinoma, Non-Small-Cell Lung; Aged; Thrombocytosis; Leukocyte Count; Survival Analysis.

ARAŞTIRMA

KÜÇÜK HÜCRELİ DIŞI AKCİĞER KANSERİ OLAN YAŞLI HASTALARDA PROGNOSTİK FAKTÖRLERİN SAĞKALIMA ETKİSİ

ÖZ

Giriş: Yeni tanı alan küçük hücreli dışı akciğer kanseri olan olguların yarısından fazlası 65 yaş üstü olgulardır ve bundan dolayı yaşlı nüfus için önemli bir sağlık sorunudur. Bu çalışmada biz küçük hücreli dışı akciğer kanseri olan 65 yaş ve üstü yaşlı hastalarda sağkalım üzerine çeşitli prognostik faktörlerin etkisini araştırmayı planladık.

Gereç ve Yöntem: Histopatolojik olarak küçük hücreli dışı akciğer kanseri tanısı konan 65 yaş ve üstü 97 olgu bu çalışmaya dahil edildi. Performans durumu, Eastern Cooperative Oncology Group 0-1 ve 2-3 olarak iki grupta ele alındı. Beyaz küre sayısı 12.0 (x 109/L)'den düşük ise normal, bu değerden fazla ise yüksek olarak sınıflandı. Benzer olarak, trombosit sayısı 400 (x 109/L)'den düşük ise normal, bu değerden fazla ise yüksek olarak sınıflandı. Mortalite riski, tek değişkenli analizde anlamlı olan tüm değişkenlerin dahil edildiği çok değişkenli Cox regresyon modeli kullanılarak analiz edildi.

Bulgular: Kaplan-Meier testi ile saptanan genel sağkalım süresi 11,2 [%95 Güven Aralığı (7.55-14.85)] aydı. Tek değişken analizde performans skoru, evre, beyaz küre ve trombosit sayısı genel sağkalımı anlamlı olarak etkiliyordu (sırasıyla p <0,001, 0,001, 0,044 ve 0,006). Çok değişkenli analizde genel sağkalım oranlarının performans skoru ve trombosit sayısı genel sağkalımı anlamlı olarak etkiliyordu (sırasıyla p <0,001 ve 0,017).

Sonuç: Küçük hücreli dışı akciğer kanseri olan yaşlı hastalarda sağkalım performans durumu, evre, beyaz küre ve trombosit sayıları tarafından anlamlı bir şekilde etkileniyordu. Bu hasta grubunda sadece yaş değil, bu faktörlerde bu hastaların tedavi planında göz önünde bulundurulmalıdır.

Anahtar Sözcükler: Küçük Hücreli Dışı Akciğer Kanseri; Yaşlı; Trombositoz; Lökosit Sayısı; Sağkalım.

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Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality in Western societies (1). NSCLC accounts for more than % 85 of all lung cancers (2). Patients often have advanced disease at the time of diagnosis. Incidence of lung cancer in elderly patients is rising due to the increased life expectancy (3). More than half of newly diagnosed patients with NSCLC are older than 65 years (4). Elderly patients are a complex group of patients with a lot of comorbidities and decreased functional capacity. NSCLC is an important public health problem in the elderly population. There is no standard treatment for this group patient with NSCLC. Moreover, limited information is available about survival and the factors associated with survival in this group of patients with NSCLC (5).

In this study, we aimed to investigate effect of various the prognostic factors on survival in NSCLC patients aged more than 65 years.

Materials and Method

Ninety-seven patients, histopathologically proven NSCLC, who are 65 years old or older, were included in this study. Impact of clinical and laboratory features on survival was analyzed retrospectively. The study was approved by the ethics committee of Kayseri Research and Education Hospital. International Union Aganist Cancer (UJCC) and American Joint Comitte on Cancer (AJCC) staging systems were used (6). Staging work-up included physical examination findings, chest plain radiographs, computed tomography (CT) scan of the chest and abdomen (in some cases abdominal ultrasonography), magnetic resonance imaging or CT of the brain, radionuclide bone scan, fiberoptic bronchoscopy, and mediastinoscopy. Data of stage, sites of metastasis, number of metastasis, performance status, routine blood tests (hemoglobin concentration, leucocyte and platelet count) were collected. Demographic data such as age, gender, smoking history, family history of cancer were also recorded.

Performance status was evaluated with the Eastern Cooperative Oncology Group (ECOG) performance status scale. Performance was graded as follows; 0: asymptomatic, 1: symptomatic, but completely ambulatory, 2: symptomatic, in bed for less than 50% of waking hours, 3: symptomatic, confined to bed or chair more than 50% of waking hours, 4: completely disabled, totally confined to bed or chair (7).

Survival was defined as the time between diagnosis and death.

Anemia was defined according to the WHO criteria, hemoglobin level below 13 g/dl in men, and 12 g/dl in women was regarded as anemia (8).

Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA). Kolmogorov-Smirnov test was used to determine normality of distributions of variables. Continuous variables with normal distribution are presented as mean ± SD. Median value is used where normal distribution is absent. Qualitative variables are given as percent. Survival rates were estimated using the Kaplan-Meier method and the log-rank test was used for the comparison of outcomes. Mortality risks were analyzed using the multivariate Cox regression model in which we included (in a backward-wald manner) all the significant variables from the univariate analysis. A p value of <0.05 was considered significant.

Results

Table 1 shows characteristics of 97 patients with NSCLC. Mean age was 72.3±5.6 (range, 65-88) years and 81 (83.5%) of 97 patients were male. Most of the patients had a history of smoking. Approximately one-third of the patients had chronic obstructive pulmonary disease (COPD). More than half of the patients had epidermoid carcinoma. Most of the patients were diagnosed with bronchoscopic biopsy and trans-thoracic fine needle aspiration biopsy. Forty-seven (48.5%) of 97 patients had anemia. At the time of analysis just 24 (24.7%) of patients were alive. Only 2 patients could be treated with surgery. Twenty-six of 44 patients with stage III disease were given curative radiotherapy. Doses of radiotherapy were 60-66 Gy. Eighteen patients received the concomitant chemotherapy consisting of docetaxel and cisplatin whereas 5 patients were given the concomitant chemotherapy consisting paclitaxel and carboplatin. The number of concomitant chemotherapy was 2 to 7 cycles. Two of stage III disease patients receiving radiotherapy were given induction chemotherapy whereas 13 patients with stage III disease received maintenance chemotherapy, the number of which was 1 to 4 cycles. Twenty-five of 53 patients with stage IV disease received palliative chemotherapy, the number of which was 1 to 6 cycles, whereas 6 patients was given palliative radiotherapy due to cranial metastases in 3 patients, bone metastasis in 2 patients, and superior vena cava syndrome in 1 patient.

Table 1— Characteristics of the Patients with NSCLC.

Age (year)	72.3±5.6
Female (%)/Male (%)	16 (16.5)/81 (83.5)
Final status	
Living (%)	24 (24.7)
Exitus (%)	73 (75.3)
History of smoking (%)	77 (79.4)
Amount of smoking in patients with positive history (package/year)	48 (10-170)
Presence of chronic obstructive pulmonary disease (%)	34 (35.1)
Family history of cancer (%)	10 (10.3)
Performance status (ECOG)	
0 (%)	14 (14.4)
1 (%)	48 (49.5)
2 (%)	21 (21.6)
3 (%)	14 (14.4)
Histology	
Non-identified NSCLC (%)	16 (16.5)
Adenocarcinoma (%)	27 (27.8)
Epidermoid carcinoma (%)	54 (55.7)
Stage	
III (%)	44 (45.4)
IV (%)	53 (54.6)
Diagnostic procedure	
Bronchoscopic biopsy (%)	59 (60.8)
Trans-thoracic fine needle aspiration biopsy (%)	29 (29.9)
Biopsy of metastasis (%)	7 (7.2)
Mediastinoscopy (%)	2 (2.1)
Hemoglobin e (g/dL)	12.67±1.89
Presence of anemia (%)	47 (48.5)
White blood cell count (x 109/L)	9.8±3.0
Platelet count (x 109/L)	304±109
Treatment	
Surgery (%)	2 (2.1)
Stage III patients	
Curative radiotherapy (%)	26 (26.8)
Concomitant chemotherapy (%)	23 (23.7)
Induction chemotherapy (%)	2 (2.1)
Maintenance chemotherapy (%)	13 (13.4)
Stage IV patients	
Palliative chemotherapy (%)	25 (25.8)
Palliative radiotherapy (%)	6 (6.2)

NSCL: non-small cell lung cancer.

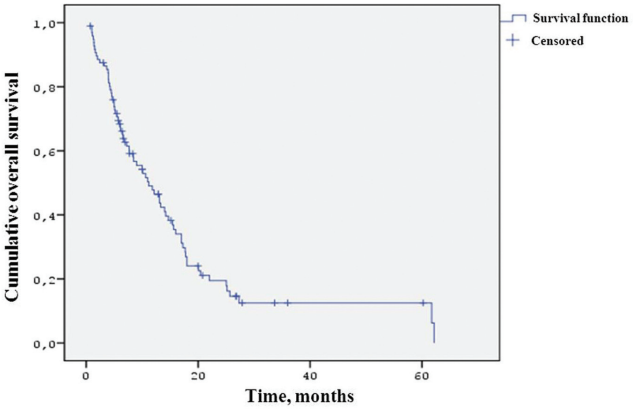

Figure 1— Overall survival by Kaplan-Meier analysis.

Table 2— Overall Survival and p Value According to Characteristics of Patients.

Factor	Overall Survival Months (95% confidence interval)	p
Gender		0.751
Female	8.5 (4.57-12.37)	
Male	11.8 (7.72-15.95)	
Stage		0.010
III	15.6 (12.17-19.03)	
IV	8.5 (4.63-12.31)	
Histology		0.490
Non-identified NSCLC (%)	6.1 (4.82-7.44)	
Adenocarcinoma (%)	12.1 (8.38-15.88)	
Epidermoid carcinoma (%)	11.8 (6.01-17.66)	
ECOG performance status		<0.001
0	17.8 (1.35-34.19)	
1	15.4 (13.04-17.76)	
2	4.6 (3.57-5.57)	
3	5.2 (1.52-8.88)	
Chronic obstructive pulmonary disease		0.735
Yes	10.1 (6.36-13.84)	
No	13.3 (4.14-22.47)	
Presence of anemia		0.276
Yes	11.0 (6.58-15.41)	
No	11.8 (4.55-19.11)	

NSCL: non-small cell lung cancer.

Overall survival was 11.2 months with Kaplan-Meier analysis (95% confidence interval 7.55-14.85) (Figure 1).

The overall survival rates according to characteristics of the patients are shown in Table 2. Stage and ECOG performance status were the characteristics that significantly influenced the overall survival (p=0.010 and p <0.001, respectively). On the other hand, gender, histology, presence of COPD and anemia did not associate with overall survival (p >0.05).

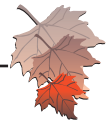

Table 3— Univariate Analysis of Risk Factors for the Overall Survival.

Risk Factor	Odds Ratio (95% confidence interval)	p
Age (year)	1.02 (0.98-1.06)	0.334
Sex (female/male)	1.11 (0.58-2.11)	0.751
Chronic obstructive pulmonary disease (yes/no)	1.09 (0.67-1.78)	0.736
History of smoking (yes/no)	1.12 (0.63-1.98)	0.699
ECOG performance score (0-1/2-3)	3.3 (2.00-5.53)	<0.001
Histology(adenocarcinoma/ epidermoid carcinoma)	1.11 (0.63-1.96)	0.726
Stage (III/IV)	1.85 (1.15-2.98)	0.011
Presence of anemia (yes/no)	1.29 (0.81-2.07)	0.279
White blood cell count (normal/high)	1.72 (1.02-2.94)	0.044
Platelet count (normal/high)	2.22 (1.26-3.91)	0.006

Univariate and multivariate analyses were performed to identify the risk factor(s) related to overall survival. Variables were classified as the most effective forms in the regression model. Patients were classified into two groups according to the performance score; ECOG 0-1 and ECOG 2-3. Histology was grouped as adenocarcinoma or epidermoid carcinoma. White blood cell (WBC) count was regarded as normal if it is lower than 12.0 (x 10^9/L), and as high if it is higher. Platelet count was regarded as normal if it is lower than 400 (x 10^9/L), and as high if it is higher. Table 3 shows the results regarding ten variables examined in univariate analysis as potential risk factors for overall survival. Four of the ten factors (ECOG performance status, stage, WBC and platelet counts) differed significantly between these groups ($p < 0.05$) in univariate analysis. All of these significant variables in the univariate analysis were included in the multivariate Cox regression to analyze mortality risk (Table 4). The multivariate Cox regression analysis identified that the overall survival rates were significantly associated with ECOG performance status (0-1 or 2-3) and platelet count (normal or high). Mortality risk was 3.21 times higher in patients with ECOG 2-3 compared to ECOG 0-1. Patients with high platelet counts had 2.01 folds higher mortality risk from those whose platelet counts were normal. In contrast, the overall survival rates were not significantly associated with stage and WBC count ($p > 0.05$).

Table 4— Multivariate Analysis of Factors Affecting on Overall Survival.

Risk Factor	Odds Ratio (95% confidence interval)	p
ECOG performance score (0-1/2-3)	3.21 (1.92-5.36)	<0.001
Stage (III/IV)	-	-
White blood cell count (normal/high)	-	-
Platelet count (normal/high)	2.01 (1.13-3.56)	0.017

Discussion

Elderly patients are a complex group of patients with a lot of comorbidities and decreased functional capacity. Cancer incidence can be different in elderly people compared with the young population, and prognosis may vary in many tumor types. For example lymphoma, over carcinoma and acute myeloid leukemia are more aggressive in elderly population while breast cancer is more indolent (9).

NSCLC is an important health problem in elder population. In this group of patient, limited information is available about survival and the factors associated with survival. In the present study we demonstrated that ECOG performance status and platelet count was associated with overall survival.

Platelets play an important role in many physiological pathways including hemostasis and inflammation. They are also closely associated with progression and prognosis of malignant tumors (10,11). Although the exact mechanism of the relationship between high platelet count and worse prognosis remains unknown, some possible mechanisms have been suggested. Thrombocytosis can promote tumor cell growth and angiogenesis (10). Thrombocytes secretes a variety of growth factors including transforming growth factor-beta (TGF-ß), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF). These growth factors can promote tumor cell proliferation and adhesion (12,13). Likewise, it has been shown that platelet-derived soluble mediators can induce invasion in different cell lines. (14). These factors are also important targets of treatment. For example, bevacizumab, an anti-VEGF monoclonal antibody, is effective in the treatment of metastatic colorectal carcinoma (15). Platelets can influence metastasis by protecting the tumor cell from host's immune system (16). Several studies have been demonstrated that pre-treatment platelet count is a novel prognostic factor in patients with NSCLC. In their study with 510 operable NSCLC patients Yu et al. have reported that the 3-year cumulative overall survival probability was 75.3% for patients with normal platelet counts and 59.2% for patients with elevated platelet counts (10). Similarly Maraz et al. have

reported that overall 5 year survival was worse in lung cancer patients with thrombocytosis, and thrombocytosis was directly correlated with the stage of cancer. They observed that the frequency of thrombocytosis was 18.6%, 19.3%, 27.5 and 28.6% in patients with tumor stages I to IV, respectively (17). In our study, thrombocytosis was a negative prognostic factor in both univariate and multivariate analysis. So it seems that a relationship between thrombocytosis and cancer is also available in elderly population.

There is a well-known relationship between cancer and inflammation. Inflammation is an important factor in tumor proliferation and prognosis (18). On the other hand, the exact mechanism(s) mediating this relationship remains unresolved. Understanding of the cause-effect relationship between inflammation and cancer may lead to significant improvements in terms of diagnosis and treatment. Tumor cells produce various cytokines and chemokines, which attract leucocytes. The inflammatory component of a neoplasm may include different types of leucocytes such as neutrophils, dendritic cells, and macrophages. These cells can produce various cytokines, cytotoxic mediators such as reactive oxygen radicals, and mediators such as tumor necrosing factor-alpha (TNF-α) and interleukins. These cells contribute carcinogenesis in the beginning of neoplastic proliferation by creating a favorable environment for tumor growth, by facilitating genomic disorders, and by activating angiogenesis. On the other hand, inflammatory responses may also be anti-tumoral, but these anti-tumoral inflammatory responses are frequently defective in cancer patients (19). In several clinical studies, it has been shown that pre-treatment WBC count and neutrophil/lymphocyte ratio, which are an indicator of systemic inflammation, are associated with poor prognosis in various types of cancer, including NSCLC. Teremuaki et al. have reported that pre-treatment neutrophil count is an independent prognostic factor in patients with advanced NSCLC. They reported an overall survival of 19.3 months for the patients with low neutrophil count, and 10.2 months for the patients with high neutrophils (20). Cedres et al. have shown that high neutrophil/lymphocyte ratio is a predictor of poor prognosis in patients with NSCLC. They reported that patients with high neutrophil/lymphocyte ratio had an overall survival of 5.6 months while patients with low neutrophil/ lymphocyte ratio had an overall survival of 11.1 months (21). In our study high leucocyte count was associated with poor prognosis in univariate analysis. Just as the thrombocytes, the relationship between leucocyte count (i.e. inflammation) and cancer prognosis in elderly population is not different from general population.

Performance status is a measure of functional capacity. A number of methods have been developed to assess the performance state. Karnofsky and ECOG performance scales are the most commonly used methods. Performance status is usually poor in elderly population compared to younger groups (22). Performance status is a predictor of overall survival in cancer patients, and it is generally used to determine cancer treatment decisions (23). Similarly, in our study, ECOG performance status significantly affected overall survival in both univariate and multivariate analysis.

The relationship between cancer stage and survival is a well-known entity. So it is not surprising that stage of cancer was associated with overall survival in univariate analysis in the present study.

Anemia is a negative prognostic factor for many types of cancer in general population. It has been shown that in patients with NSCLC anemia have negative effects on quality of life, increased hospitalization, , as well as survival (24). On the other hand, in our study, anemia was not a prognostic factor associated with survival. We suggest that anemia is not a factor affecting prognosis in elderly population.

In general population, overall survival in advanced NSCLC is 10-23 months for stage 3, and 6-18 months for stage 4 cancer (25). In our study, overall survival was 15.6 months for patients with stage 3, and 8.5 months for patients with stage 4. We suggest that elderly patients with NSCLC have a similar overall survival in general population. Therefore, it should be to consider performance status and other parameters rather than age in the treatment decisions of patients with advanced NSCLC.

In conclusion, overall survival was associated with performance status, stage of cancer, leukocytosis, and thrombocytosis in elderly patients with NSCLC. In this group of NSCLC patients, these factors rather than age should be taken into consideration in treatment planning.

Conflict of Interest

The authors have no financial disclosures to declare and no conflicts of interest to report.

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