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Adjuvant Chemotherapy in Elderly Patients with Early-stage Non-small Cell Lung Cancer

Yaşlı Küçük Hücreli Dışı Akciğer Kanseri Hastalarında Adjuvan Kemoterapi

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ABSTRACT

Objective: Early-stage non-small cell lung cancer (NSCLC) constitutes approximately 25-30% of newly diagnosed lung cancers. Elderly patients with NSCLC have generallly been underrepresented in clinical studies. We explored adjuvant chemotherapy results in patients ≥65 years with early-stage NSCLC.

Methods: The medical records of 111 elderly patients with early-stage NSCLC were reviewed retrospectively. Collected data included demographic information, clinical assessments and information on treatment. Survival was estimated using the Kaplan-Meier method and prognostic factors were evaluated with log-rank and Cox regression tests.

Results: The median disease-free survival (DFS) was 22.6 months. In univariate analysis, significant association between stage, performance score (PS), adjuvant chemotherapy and DFS was detected ($p<0.05$). Stage, PS and adjuvant chemotherapy were found to have significant effects on overall survival (OS) ($p<0.05$). The median survival for the entire group was 41.6 months. Multivariate analysis showed that stage, PS and adjuvant chemotherapy affected both DFS and OS.

Conclusion: Survival of elderly patients with early-stage NSCLC was significantly influenced by stage, PS and adjuvant chemotherapy. These factors, rather than age, should be considered in the treatment planning for elderly patients with NSCLC.

Keywords: Adjuvant, elderly, non-small cell lung cancer

ÖZ

Amaç: Tanı anında akciğer kanserlerinin %25-30'u erken evre küçük hücreli dışı akciğer kanseridir (KHDAK). Yaşlı hastalar klinik çalışmalarda yeteri kadar temsil edilmemişlerdir. Bu çalışmada 65 yaş üstü erken evre KHDAK'li hastalarda adjuvan kemoterapi sonuçlarını araştırdık.

Yöntemler: Türkiye'de iki ayrı merkezde 111 yaşlı erken evre KHDAK'li hastanın kayıtları retrospektif olarak incelendi. Toplanan kayıtlar demografik özellikleri, klinik değerlendirmeleri ve tedavi sonuçları ile bilgileri içermekte idi. Sağkalım Kaplan-Meier metodu ile ve prognostik faktörler log-rank ve Cox regresyon testleri ile değerlendirildi.

Bulgular: Medyan hastalıksız sağkalım 22,6 ay idi. Tek değişkenli analizlerde, hastalıksız sağkalım ile evre, performans skoru (PS), adjuvan kemoterapi arasında anlamlı ilişki mevcuttu ($p<0,05$). Genel sağkalım ile evre, PS ve adjuvan kemoterapi arasında anlamlı ilişki bulundu ($p<0,05$). Tüm grup için genel sağkalım 41,6 ay idi. Çok değişkenli analizlerde evre, PS ve adjuvan kemoterapi ile genel sağkalım ve hastalıksız sağkalım arasında anlamlı ilişki saptandı ($p<0,05$).

Sonuç: Yaşlı erken evre KHDAK'li hastaların sağkalımını evre, PS ve adjuvan kemoterapi etkilemektedir. Tedavi planına karar verilirken sadece yaşın değil bu faktörlerin de değerlendirilmesi gerekir.

Anahtar Sözcükler: Adjuvan, yaşlı, küçük hücreli dışı akciğer kanseri

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Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths in the US. A total of 224.390 new lung cancer cases and 158.080 deaths from lung cancer were expected to occur in the United States in 2016 (1). In Turkey, lung cancer is the leading cause of cancer in men in all age groups and in male patients older than 50 years. It is the fourth common cause of all cancers in women in all age groups and third common cause in female patients older than 50 years (2). Approximately 85% of all lung cancers are non-small cell, and majority of these cases are metastatic or advanced at diagnosis (3).

Between 2010 and 2030, a 67% increase in cancer incidence is anticipated for patients aged ≥65 years (4). Specifically, half of the newly diagnosed NSCLC cases occur in patients aged ≥65 years (5). Additionally, elderly patients suffer from approximately twice as many comorbidities compared with the general population which may have a considerable impact on their health and performance status (6).

In clinical trials, the definition of an elderly patient remains controversial. Epidemiologic literature uses an age of 65 years for the selection of elderly patients (7). It should be noted, however, that there is little knowledge regarding the management of resected elderly patients with NSCLC (8). Therefore, in this study we evaluated the patients ≥65 years of age with surgically resected early-stage NSCLC who had also received adjuvant chemotherapy.

Methods

We retrospectively analyzed the records of the 111 patients who were aged ≥65 years with NSCLC from December 2005 to January 2015 at the Dr. Lütfi Kırdar Kartal Training and Research Hospital and Kocaeli University School of Medicine. Ethics committee approval was obtained from the local committee. Written informed consent was not obtained from patients due to the retrospective nature of the study. All medical records were collected through a detailed review of the patients'charts. The data included demographics, histology, staging, presenting symptoms, treatments, toxicities, and treatment side-effects. TNM classification (7th edition) was used for staging of the patients. Eastern Cooperative Oncology Group (ECOG) performance score (PS) was used for the detection of performance status (9).

These 111 patients that underwent surgery (all of the patients) had no significant comorbidities. Of these, patients who did not receive chemotherapy had stage 1A disease and 1B disease with good prognostic criteria. Eight patients were not given chemotherapy because of having a poor PS after surgery. Nineteen patiens with a good PS had stage 1B disease with poor risk factors and stage 2 disease did not receive chemotherapy. Therefore, out of 111 patients, 84 patients received chemotherapy and these 84 patients were compared with these 19 patients who were offered but did not receive chemotherapy. The response to therapy was determined according to the Response Evaluation Criteria in Solid Tumors criteria (10).

Statistical Analysis

SPSS 17.0 (SPSS Inc., Chicago, IL, USA) software was used for all statistical analyses. A p value ≤0.05 was considered to be significant. Toxicity was classified according to the World Health Organization criteria at each cycle of chemotherapy (11). Kaplan-Meier curves were used for the disease-free survival (DFS) and overall survival (OS) analysis and the log-rank test was used for comparisons. A Cox proportional hazard analysis was conducted in order to calculate hazard ratios [95% confidence interval (CI)]. DFS was calculated from the diagnosis of the patient to the date of disease progression, recurrence or death from any cause. OS was calculated from the diagnosis of patient to the date of death from any cause or to the date of the last follow-up.

Results

Data from 111 patients aged ≥65 years old were collected. Ninety-three patients (83.8%) were male and 18 (16.2%) were female. The median age of the patients was 68.0 years (range=65-82 years). Patients had no significant comorbidities. Thirty-eight patients (34.2%) had hypertension, 6 patients had thyroid disorders (5.4%), 5 had renal disease (4.5%) that were easily managable. In the histopathological examinations, 61 (54.9%) of tumors (patients) were detected as squamous cell carcinoma and 33 (29.7%) were adenocarcinoma. Eighty-one percent of the patients were managed with lobectomy, and 19% with segmentectomy or wedge resection. Forty-five percent of the patients had clinical stage 1 and 55% had stage 2 disease. A PS score of 0-1 and 2-4 were recorded in 74.7% and 9.0% of the patients, respectively. Two-thirds of the patients had a smoking history. Approximately, one-third of the patients (32.4%) experienced a weight loss of ≥5% in the last 3 months.

Patients who did not receive chemotherapy, had stage 1A disease and 1B disease with good prognostic criteria and patients with poor PS after surgery did not receive chemotherapy. Therefore, 84 of 111 elderly patients with NSCLC who were eligible for chemotherapy received it. Nineteen patients with poor risk stage 1B disease and stage 2 disease did not receive chemotherapy (Table 1). There were no differences between the characteristics of the patients (p>0.05) (Table 1). Only 9 patients (10.7%) with a PS of 2 received single-agent chemotherapy and 75 patients (89.3%) received combination chemotherapy. Overall, carboplatin-based combinations (51.1%) were most commonly administered. Thirty-six of these 84 patients (42.9%) were treated with carboplatin-paclitaxel, 26 were treated with cisplatin-vinorelbine (31.0%), 4 were treated with carboplatin-vinorelbine (4.7%), 6 were treated with cisplatin-docetaxel (7.1%), 3 were treated with cisplatin-gemcitabine (3.6%), 3 were treated with single-agent docetaxel (3.6%) and 6 were treated with single-agent gemcitabine (7.1%). There were no differences between combination arms regarding to DFS or OS (p>0.05). Seventy-two patients (85.7) that received chemotherapy had ≥3 cycles of chemotherapy. The most frequent toxicities were hematological toxicities (40.4%), nausea-vomiting (22.6%) and neurological toxicities (11.9%). Treatment results are given in Table 2.

The median survival for the overall patient population was 41.6 months (95% CI=33.4-49.8) with a 5-year survival rate of 29.5% (Figure 1). In univariate analysis, stage, PS, adjuvant chemotherapy, and combination chemotherapy significantly affected OS. Patients that received adjuvant chemotherapy showed a significant longer OS (36.1 months vs. 56.4 months, p<0.01) (Figure 1). Patients who received combination therapy showed better survival outcomes than the patients who received single-agent therapy (48.4 months vs. 42.7 months; p<0.05). The median survival of the patients with stage 1 disease was longer than patients who had stage 2 disease (54.4 months vs 34.5 months, p<0.01). The median survival of the patients with a PS of 0-1 was longer than the patients with a PS of 2-4 (46.7 months vs 22.4 months, p<0.01). There were no relationships detected between weight loss, gender, smoking, histopathology, and OS (p>0.05). These data are shown in Table 3.

In multivariate analysis, PS, stage, and adjuvant chemotherapy showed a consistent relationship with OS and DFS (p<0.05) (Table 4). The median DFS was 22.6 months (95% CI=16.7-28.4). Patients that received adjuvant chemotherapy showed a significantly longer DFS (24.1 months vs. 22.5 months, p<0.01). In univariate analysis, significant associations between stage, PS, adjuvant chemotherapy, and DFS were detected (p<0.05) (Table 3).

Table 1. Characteristics of the patients

Characteristic	Patients (n=84)*	Patients (n=19)±	
Sex			
Male	67 (65.0%)	12 (11.7%)	*p*>0.05
Female	17 (16.5%)	7 (6.8%)	
Age			
Median (range)	67.6 (65-80)	68 (67-82)	*p*>0.05
ECOG PS			
0-1	75 (72.8%)	14 (13.5%)	*p*>0.05
2-4	9 (8.7%)	5 (5.0%)	
Weight loss			
≥5% in previous 3 months	24 (23.3%)	5 (5.0%)	*p*>0.05
≤5% in previous 3 months	60 (58.2%)	14 (13.5%)	
Smoking habitus			
Current or former	63 (61.1%)	12 (12.0%)	*p*>0.05
Never	21 (20.3%)	7 (6.6%)	
Histology			
Squamous cell	52 (50.4%)	12 (11.7%)	*p*>0.05
Adenocarcinoma	20 (19.4%)	6 (5.8%)	
Others	12 (11.7%)	1 (1.0 %)	
Stage			
1	38 (36.8%)	8 (7.8%)	*p*>0.05
2	46 (44.6%)	11(10.8%)	

*Patients that received chemotherapy, ±Patients that did not receive chemotherapy, ECOG PS: Eastern Cooperative Oncology Group Performance Status

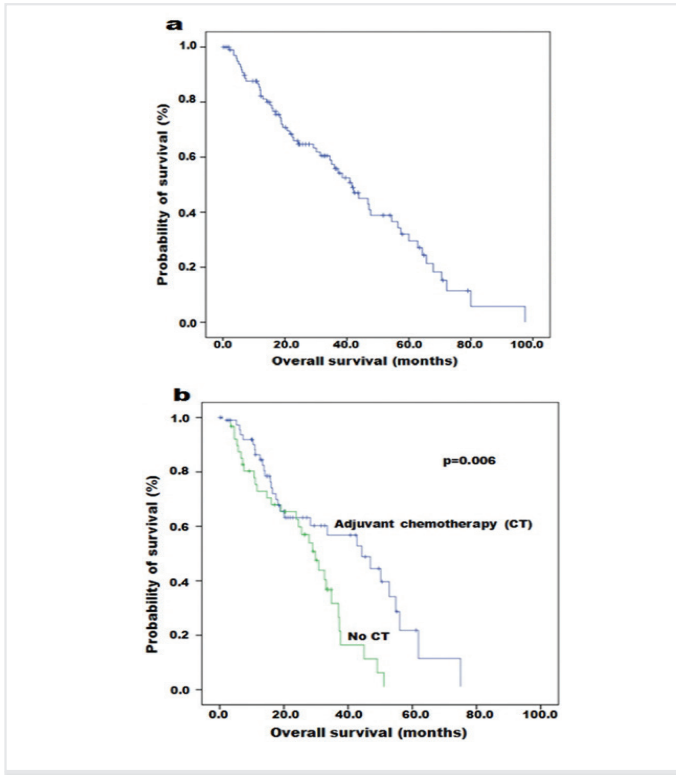

Figure 1. a) Median survival of the patients, b) Survival of the patients who did not receive adjuvant chemotherapy
CT: Chemotherapy

Table 2. Chemotherapy modalities and toxicities of the patients

	Patients (n=84)	(%)
Chemotherapy regimen		
Combination	75	(89.3%)
Single agent	9	(10.7%)
Combination therapy		
Carboplatin-paclitaxel	36	(42.9%)
Carboplatin-vinorelbine	4	(4.7%)
Cisplatin-docetaxel	6	(7.1%)
Cisplatin-gemcitabine	3	(3.6%)
Cisplatin-vinorelbine	26	(31.0%)
Docetaxel	3	(3.6%)
Gemcitabine	6	(7.1%)
Chemotherapy cycles		
<3	12	(14.3%)
≥3	72	(85.7%)
Toxicities		
Hematological	34	(40.4%)
Nausea-vomiting	19	(22.6%)
Neurological	10	(11.9%)

In multivariate analysis, PS, stage, and adjuvant chemotherapy affected DFS (Table 4).

Discussion

Elderly patients represent a complex group based on their comorbidities and reduced functional reserves. Lung cancer is an important health issue in this population (12-15). To date, there has been no standard therapy accepted for NSCLC in the elderly; however JBR 10 trial and the meta-analysis of the Lung Adjuvant Cisplatin Evaluation and JBR 10 trials suggested that elderly patients benefited from treatment with acceptable toxicity (13-15). It is predicted that there will be 67% more patients with lung cancer ≥65 years by 2030. Therefore, in this study we adressed our adjuvant treatment results in elderly patients with resected early-stage NSCLC.

The results of previous studies have demonstrated the benefit of chemotherapy in elderly patients with resected NSCLC (16). Früh et al. (15) showed that adjuvant cisplatin-based chemotherapy should not be withheld from elderly patients with NSCLC purely on the basis of age. Although our study included only small number of patients, our results were commensurate with the results of the aforementioned studies, all of which indicated that adjuvant chemotherapy and combination chemotherapy were well-tolerated and provided clinical benefits in elderly patients with early-stage NSCLC.

Patients treated with adjuvant chemotherapy had higher DFS and OS. Cisplatin- and carboplatin-based combination chemotherapy appeared to be tolerated well. In the database analysis conducted by Cuffe et al. (13), 3759 patients ≥65 years receiving adjuvant chemotherapy showed better OS.

Table 3. Univariate analysis between clinopathological characteristics of the patient group and OS and DFS

Variable	Disease free survival		Overall survival	
	Median (months)	p value	Median (months)	p value
Stage				
1	24.7	0.01	54.4	0.004
2	19.6		34.5	
Performance status				
0-1	24.9	0.001	46.7	0.008
2-4	16.8		22.4	
Weight loss				
≤5% in previous 3 months	23.7	0.078	48.7	0.092
≥5% in previous 3 months	20.1		39.6	
Adjuvant chemotherapy				
Yes	25.2	0.002	56.4	0.006
No	19.7		36.1	
Chemotherapy regimen				
Combination	24.9	0.06	48.4	0.042
Single agent	20.1		42.7	
Smoking history				
Yes	22.6	0.28	35.7	0.078
No	24.8		47.7	
Tumor histology				
Squamous cell	23.6	0.224	43.0	0.146
Others	21.8		39.7	

OS: Overall survival, DFS: Disease-free survival

Table 4. The multivariate analysis between clinopathological characteristics of the patients and OS and DFS

	Disease-free survival			Overall survival		
Variables	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Performance status	0.079	0.008-0.842	0.033	0.074	0.008-0.830	0.022
Adjuvant chemotherapy	0.072	0.007-0.825	0.024	0.078	0.007-0.826	0.016
Stage	0.080	0.009-0.840	0.044	0.080	0.007-0.854	0.038

OS: Overall survival, DFS: Disease-free survival

Although JBR 10 confirmed a survival benefit for cisplatin-vinorelbine in patients ≥65 years, we found a trend towards using carboplatin-based combinations (14). These findings are consistent with those of a new study conducted in 2789 patients with resected NSCLC (16). When platinum chemotherapies were compared, superiority with respect to toxicities and efficacy were not detected. Similar findings were detected in two recent population-based analyses (13,17). Collectively, these results indicate that patients ≥65 years with resected early-stage NSCLC benefit from adjuvant chemotherapy.

Approximately 25-30% of all NSCLC cases are diagnosed at an early stage (18). With the increasing usage of computed tomography, the incidence of early cancers is expected to increase (19). Surgical removal at this early stage represents the maximal opportunity for long term survival in lung cancer (20). Five-year relative survival rates for localized lung cancer were 54% and 26.5% for regional lung cancer (21). Five-year survival after lobectomy for stage 1 NSCLC was found to range from 45% to 65%, depending on the stage and the location of the cancer (22). Demirci et al. (23) evaluated 26 patients with NSCLC who were older than 70 years and underwent surgery and received adjuvant treatment. The median OS was 21.8 months for stage 1B, 35.4 months for stage 2A, 27.6 months for stage 2B and 21.8 months for stage 3A disease (23). In our study, the median survival for the total study population was 41.6 months with a 5-year survival rate of 29.5%. The median survival of the patients with stage 1 and 2 disease were 54.4 and 34.5 months with 5-year survival rates of 45.9% and 27.1%, respectively. Consistent with the aforementioned studies, our results confirmed the importance of stage.

Performance status is a predictor of OS in cancer patients, and is generally used to inform cancer treatment decisions (24,25). Inal et al. (24) evaluated prognostic factors for OS in elderly (≥65 years) patients with advanced NSCLC who received first-line cisplatin-based chemotherapy. They found PS as an important prognostic factor in elderly patients with advanced NSCLC (24). Also, the PS has already been considered as an important prognostic factor in elderly patients with advanced NSCLC in other studies (25,26). Unal et al. (25) investigated the effect of various the prognostic factors on survival in NSCLC patients ≥65 years. They found that PS in addition to stage and white blood cell and platelet count significantly influenced survival (25). In our study, we determined the importance of PS on survival in early-stage NSCLC for both DFS and OS.

Patients with comorbidity do not receive standard cancer treatments such as surgery, chemotherapy, and radiation therapy as often as patients without comorbidity, and their chance of completing a course of cancer treatment is lower (27). In our study, we observed that patients that were chosen for operation were carefully selected patients that had minimal comorbidities. This may cause bias for our results. Another limitation of our study was having limited number of patients especially compared with recently published studies (16). This may explain the relatively lower survival times compared with these studies.

Based on our study results, we recommend the usage of combination chemotherapy regimens in elderly patients with a good PS. It is important to note that the type of adjuvant chemotherapy used did not have an impact on survival. In conclusion, adjuvant chemotherapy should not be withheld based on age alone in patients with early-stage NSCLC.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the local committee.

Informed Consent: Written informed consent was not obtained from patients due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.K., S.K., D.I., U.I., Design: U.K., S.K., K.U., Data Collection or Processing: S.K., D.I., A.S., Ö.A., Analysis or Interpretation: U.K., U.I., D.A., A.S., Ö.A., Ö.O., Literature Search: S.K., D.I., A.S., U.A., U.I., D.A., E.Ö., K.U. Writing: U.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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