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ORIGINAL PAPER

Prognostic factors in elderly patients with non-small cell lung cancer: a two-center experience

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Abstract Non-small cell lung cancer (NSCLC) is usually at advanced stage when it is diagnosed. There is no consensus about the standard treatment in elderly patients with advanced NSCLC. Generally, data regarding elderly patients with NSCLC are withdrawn from general NSCLC studies based on subgroup analyses and suggestions. We evaluated prognostic factors in elderly patients with advanced NSCLC. We reviewed retrospectively 338 patients from August 2005 to July 2009 in two centers in Turkey. Medical records of the patients ≥65 years with advanced NSCLC were collected. Collected data included demographic informations, clinical assessments and information on treatment, toxicities and outcomes. Survival was estimated by using Kaplan–Meier method and prognostic factors were evaluated with log-rank and Cox regression tests. The median overall survival (OS) for the entire group was 15.4 months (95% CI: 12.7–18.0). In univariate analysis, weight loss, stage, combination therapy, second-line chemotherapy and tumor response ($P < 0.01$) and performance status significantly affected OS ($P < 0.05$). The median progression-free survival (PFS) was 10 months (95% CI: 8.4–11.6). In univariate analysis, there was only a significant association between tumor response and PFS (14.6 vs. 8.5 months; $P < 0.001$). Multivariate analysis showed that only response to therapy was an important prognostic factor for OS ($P < 0.001$). Survival of elderly patients with advanced NSCLC is significantly influenced by performance status, weight loss, stage, combination therapy, second-line chemotherapy and response to therapy. Not only age but also these factors may be kept in mind in the treatment planning of the elderly patients with NSCLC. These results may be of benefit in changing clinical practice in elderly patients with NSCLC who are often undertreated.

Keywords Elderly patients · Lung cancer · Neoplasm · Non-small cell lung cancer · Prognostic factors

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Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths in the Western countries [1]. NSCLC is usually at advanced stage when it is diagnosed. A total of 219,440 new lung cancer cases and 159,390 deaths from lung cancer are projected to occur in the United States in 2009 [2]. NSCLC accounts for more than 85% of all lung cancers [3].

The incidence of lung cancer in elderly patients is rising because of the increased life expectancy [4]. About 50% of newly diagnosed NSCLC cases occur in patients aged more than 65 [5]. Therefore, it is an important health burden on the aging populations. Although 50% of elderly patients with NSCLC have a good performance status (PS), they are being treated with lower rates of definitive treatment [6]. Performance status and clinical stage of disease did not differ greatly in a review of 5,404 patients with lung cancer according to the age older than 50 and below 50 years

although younger patients received more aggressive treatment while elderly patients did not [7].

There is still no agreement about the standard treatment in elderly advanced stage patients with NSCLC and which factors affect the survival in elderly patients with lung cancer. This study was planned to report the prognostic factors in our patients older than 65 years with NSCLC. We aimed to identify the prognostic factors that could be useful in better selection of treatment modalities in elderly patients with NSCLC.

Materials and methods

We retrospectively analyzed the records of the elderly patients with NSCLC from August 2005 to July 2009 at the Dr. Lutfi Kirdar Education and Research Hospital and Kocaeli University Medical Faculty. According to the data from the Turkish Statistical Institute, the life expectancy at birth of the Turkish people for men is 69.5 and for women is 74 years; therefore, elderly patients with NSCLC ≥65 years were included in this study [8]. All medical records were collected by a detailed review of the patients' charts whether they have received a treatment of palliative or curative intent. The data included demographic information, histologic classification, clinical staging, presenting symptoms and treatment modalities. The diagnosis of NSCLC was established mostly by bronchoscopic biopsy and then by transthoracic fine needle aspiration biopsy (TTIAB) or mediastinoscopy, respectively. Complete blood count, liver function tests, LDH value, renal function tests before the start of chemotherapy and before each cycle were all recorded. Toxicities and treatment side effects were obtained from patients' records that were all recorded before each chemotherapy cycles. All patients were staged according to the TNM classification based on the physical examination, chest X-ray, chest CT scans, abdominal ultrasound or CT, bone and brain scans. Performance status was recorded according to the Eastern Cooperative Oncology Group (ECOG) performance score [9]. Sites of distant metastases were recorded. Patients were treated according to stage and performance status as chemotherapy, radiotherapy or combination modalities. Patients with stage IV NSCLC were treated chemotherapy if the PS was less than two. Radiotherapy was performed as concurrent therapy or as palliative therapy when needed. Data on the chemotherapy regimen, number of cycles, toxicity, objective response, second-line therapy, the time of disease progression and death were all collected. The response to therapy was assumed Response Evaluation Criteria in Solid Tumors (RECIST) criteria as partial, when tumor size decreased 30% radiologically. If tumor size was not changed after treatment defined as stable disease and if tumor size increased 20%, it was accepted as progressive disease [10]. The patients were followed until their death or last follow-up.

Statistical analysis

SPSS 16.0 (SPSS Inc., Chicago, IL, USA) software was used for the statistical analyses. A P value less than 0.05 was considered to be significant. Most values were expressed as mean ± SD. Median and minimum–maximum levels were used when data were not normally distributed. The variables considered were sex, PS, weight loss, smoking habitus, histology, stage of disease, chemotherapy regimens, number of cycles and second-line chemotherapy. Toxicity was classified according to the World Health Organization criteria at each cycle of chemotherapy [11]. Kaplan–Meier method was used for survival analysis. The univariate analysis of potential prognostic factors was assessed but using the log-rank test. The Cox regression model was used for multivariate analysis. Overall survival (OS) was calculated from the diagnosis of patient to the date of death from any cause or of the last follow-up. Progression-free survival (PFS) was calculated from the diagnosis of patient to the date of disease progression, recurrence or death from any cause.

Results

A total of 338 elderly patients with NSCLC were eligible including 300 male and 38 female patients. The median age of the patients was 69.4 (range 65–89). Eighty-five percent of the patients had a smoking history. In histopathological examination, 135 (39.9%) of tumor were detected as squamous cell carcinoma and 88 (26%) of them were adenocarcinoma. No pathologic discrimination was done in other patients. PS score of 0–1 was stratified in 70.8%, and PS score of 2–4 was recorded in 29.2% of the patients. Fifty-four percent of patients (53.8%) had a weight loss of ≥5% in the last 3 months. Fifty-three percent of the patients were clinically staged as stage III, and 47% of the patients were stage IV. Patient characteristics are shown in Table 1.

Two hundred and twenty-two patients (65%) received combination chemotherapy and 30 patients (9%) received single-agent chemotherapy. Out of 217 (64.2%) of patients were given platinum-based combination therapy mostly as carboplatin–paclitaxel (29%), carboplatin–docetaxel (7.4%), carboplatin–gemcitabine (7.4%), cisplatin–docetaxel (9.5%), and cisplatin–gemcitabine (6.5%). Sixty-one percent of the patients that received chemotherapy had ≥3 cycles of chemotherapy. The number of patients with a PS score 0–1 that received ≥3 cycles was 151 (59%) and only

Table 1 Characteristics of the patients

Characteristic	Patients ($n = 338$)
Sex	
Male	300 (88.8%)
Female	38 (11.2%)
Age	
Median (range)	69.4 (65–89)
ECOG PS	
0–1	233 (68.9%)
2–4	105 (31.1%)
Weight loss	
≥5% in previous 3 months	182 (53.8%)
≤5% in previous 3 months	156 (46.2%)
Smoking habitus	
Current or former	255 (75.4%)
Never	83 (24.6%)
Histology	
Squamous cell	135 (39.9%)
Adenocarcinoma	88 (26.0%)
Stage	
3	179 (53%)
4	159 (47%)

28 patients (11%) with a PS score of 2–4 received ≥3 cycles of chemotherapy. The most frequent toxicities were the haematological (44.2%), nausea–vomiting (23.5%) and neurological (10.8%) toxicities. The most common grade 3/4 haematological toxicities were neutropenia (34.6% for combination therapy vs. 14.3% for single-agent chemotherapy, $P = 0.03$) and anemia (20.3% for combination therapy vs. 8.4% for single-agent chemotherapy, $P = 0.046$). Treatment results are given in Table 2.

The overall response rate (sum of partial and complete response rates) was 47.6%. The response rate of the patients that received combination chemotherapy was 51.3% (114 of 222) and this was 20% (6 of 30) for single-agent chemotherapy. Second-line therapy was administered to 67 patients (19.8%). Thirty-seven of the patients (55%) received single-agent chemotherapy and 30 patients (45%) received combination chemotherapy in the second-line therapy. In the second-line therapy, mostly gemcitabine (17.9%) and docetaxel (17.9%) were used as single-agent therapy, and cisplatin–gemcitabine (10.4%) and carboplatin–paclitaxel (7.4%) were used as combination therapy (Table 2).

The median survival for the entire group was 15.4 months (95% CI: 12.7–18.0; Fig. 1) with 1- and 2-year survival rates of 58.4% and 25.4%, respectively. By July 2009, 168 (49.7%) of patients were dead. The median follow-up for survivors was 10.7 months. In univariate analysis, weight loss, stage, combination therapy, second-line chemotherapy and response to therapy significantly affected OS ($P < 0.01$). Also, PS correlated with a better OS ($P < 0.05$). The median survival of the patients who had a PS 0–1 (17.0 vs. 10.8 months; $P < 0.05$) and who had stage III disease (18.4 vs. 11.1 months; $P < 0.01$) was longer than the patients who had a PS 2–4 and stage IV disease (Figs. 2, 3). Patients that received combination therapy showed better survival than the patients who received single-agent therapy (18.4 vs. 14.7 months;

Table 2 Treatment modalities and regimens of the patients

	Patients (n) (%)
Chemotherapy regimen	
Combination	222 (65.7%)
Single agent	30 (8.90%)
Best supportive care	86 (25.4%)
Combination therapy	
Carboplatin–paclitaxel	98 (29%)
Carboplatin–docetaxel	25 (7.4%)
Carboplatin–gemcitabine	25 (7.4%)
Carboplatin–vinorelbine	1 (0.3%)
Cisplatin–docetaxel	32 (9.5%)
Cisplatin–gemcitabine	22 (6.5%)
Cisplatin–vinorelbine	9 (2.7%)
Cisplatin–paclitaxel	5 (1.5%)
Cisplatin–etoposide	2 (0.6%)
Docetaxel–gemcitabine	2 (0.6%)
Gemcitabine–vinorelbine	1 (0.3%)
Chemotherapy cycles	
<3	45 (18%)
≥3	207 (82%)
Response to therapy	
Yes (Partial or complete response)	161 (63.8%)
No	91 (36.2%)
Second-line therapy	67 (26.5%)
Gemcitabine	13 (19.4%)
Docetaxel	12 (17.9%)
Cisplatin–gemcitabine	7 (10.4%)
Cisplatin–paclitaxel	5 (7.46%)
Cisplatin–etoposide	4 (5.97%)
Carboplatin–docetaxel	2 (2.98%)
Vinorelbine	2 (2.98%)
Cisplatin–docetaxel	1 (1.49%)
Carboplatin–gemcitabine	1 (1.49%)
Carboplatin–vinorelbine	1 (1.49%)
Paclitaxel	1 (1.49%)
Toxicities	
Haematological	111 (44.2%)
Nausea–vomiting	59 (23.5%)
Neurological	27 (10.8%)

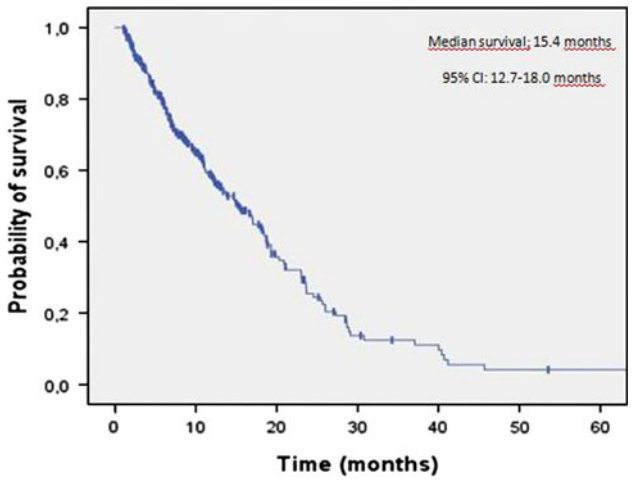

Fig. 1 Median survival time of the patients

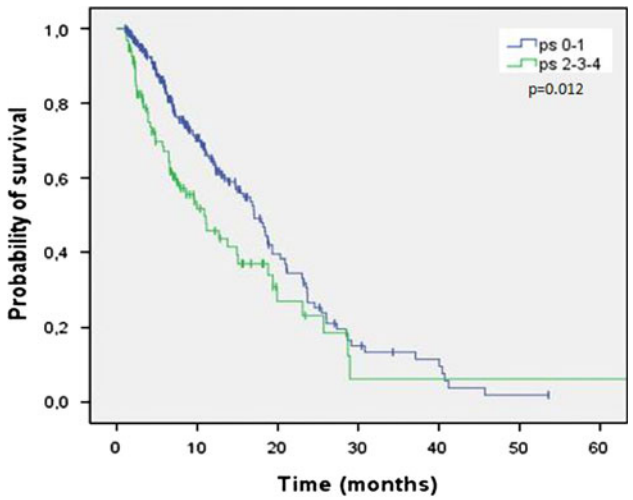

Fig. 2 Survival of the patients according to the performance status (PS)

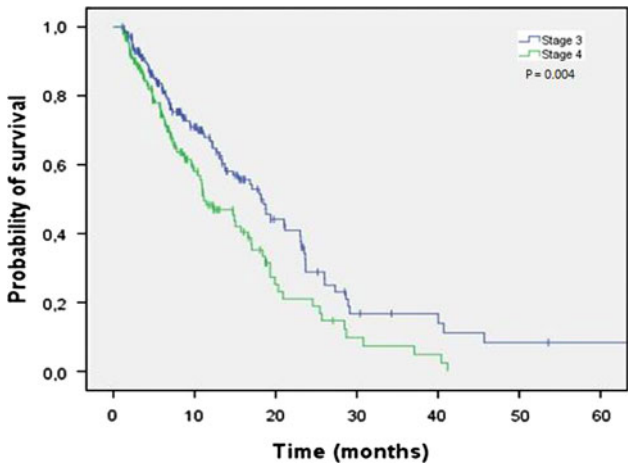

Fig. 3 Survival of the patients according to the stage

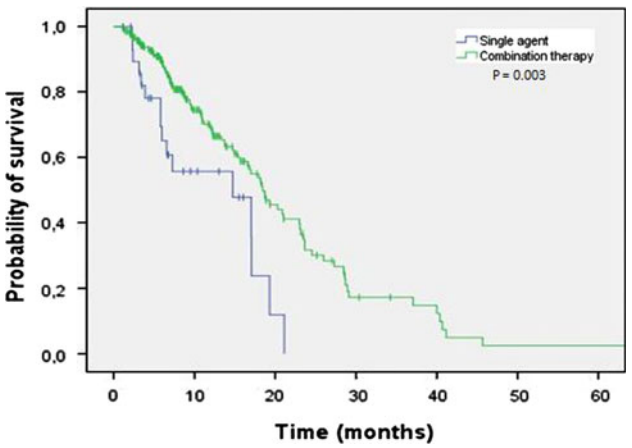

Fig. 4 Survival of the patients according to the chemotherapy

$P < 0.01$; Fig. 4). There was no relationship between sex, LDH and hemoglobin values, smoking history, histology of the tumor, chemotherapy cycle and overall survival ($P > 0.05$). These data are shown in Table 3. In multivariate analysis, only response to therapy showed consistency with survival ($P < 0.001$).

The median PFS was 10 months (95% CI: 8.4–11.6). In univariate analysis, there was only a significant association between tumor response and PFS (14.6 vs. 8.5 months;

Table 3 Univariate analysis of the prognostic factors

Variable	Overall survival	
	Median (months)	*P* value
Stage		
3	18.4	0.004
4	11.1	
Performance status		
0–1	17.0	0.012
2–4	10.8	
Weight loss		
≤5% in previous 3 months	13.0	0.004
≥5% in previous 3 months	23.6	
Chemotherapy regimen		
Combination	18.4	0.003
Single agent	14.7	
Platinum-based therapy		
Cisplatin	20.3	0.374
Carboplatin	16.8	
Tumor response		
Yes	23.0	0.000
No	14.7	
Second-line therapy		
Yes	23.0	0.000
No	14.7	

$P < 0.001$). In multivariate analysis, there was no relationship found between variables and PFS.

Discussion

Elderly patients are a complex patient group with their comorbidities and reduced functional reserves. NCSLC represents a significant health problem in the elderly population. There is no standard treatment accepted for the NSCLC. Frasci et al. [12] showed better survival of the patients treated with combination therapy versus single-agent therapy in 120 elderly patients. In 1980s and 1990s, cisplatin-based chemotherapy was the standard treatment of advanced NSCLC [13]. Langer et al. [14] suggested that platinum-based therapy can be used in elderly patients with NSCLC. Lilenbaum et al. [15] randomized elderly patients to receive paclitaxel or paclitaxel and carboplatin. Although it was not statistically significant, the subgroup of the elderly patients showed that combination arm had a better median survival time. In our study, 65% of our patients received combination therapy. The number of patients that received platinum-based combination therapy was 217 (64.2%). Carboplatin-based therapy was preferred as a first-line therapy in patients with decreased renal function, and nephrotoxicity frequency was low. Cisplatin-based regimen as a first-line treatment was administered to the patients with a good performance status and normal renal function. Single-agent cytotoxic drugs were preferred in elderly patients with marked weight loss and decrease oral intake. As these studies stated above, the combination therapy arm in our study showed a better survival than single-agent chemotherapy. But when the platinum chemotherapies are compared, there were no advantages of each agent to each other with respect to toxicities and efficiency. Haematological toxicity was the major toxicity. Combination arm therapy showed more neutropenia and anemia in our study ($P < 0.05$).

There are a few studies investigating prognostic factors in elderly with advanced NSCLC. Elderly patients with a good performance status are considered candidates for platinum-based combination therapy [16]. Also, Chen et al. [17] found a better prognosis in elderly patients with NSCLC with a good performance status. Our results were consistent with these previous studies. Weight loss, chemotherapy cycle, stage, tumor response and comorbidities were found significant prognostic factors in other studies [12, 18, 19]. We also found the importance of these factors on the survival of elderly patients with NSCLC as in these studies. Li et al. [19] demonstrated that second-line therapy was a strong predictor of survival in elderly patients with advanced NSCLC. Although there was no previous studies showing significancy of second-line treatment on survival in elderly patients with NSCLC, this and our study results may be an encouragement in favor of using more second-line therapies.

In univariate analysis of PFS and OS, response to therapy was found to be significant. Moreover, multivariate analysis also showed that response to therapy was an independent prognostic factor. Li et al. [19] demonstrated that tumor response to therapy showed a survival benefit. This result may be regarded as a determinant of continuation, modification or cessation of the treatment especially in elderly patients who cannot tolerate the chemotherapy regimen.

In conclusion, while new studies are done about the prognostic factors in elderly patients with advanced NSCLC, we recommend the usage of more aggressive chemotherapy regimens in these patients especially if they have a good performance status and a weight loss of $\leq$5% in previous 3 months. Response to therapy may influence the decisions about the continuation of first-line therapy and selection of the patients that can be given second-line therapy. When deciding a treatment strategy, physicians should be aware of these favorable prognostic factors and these factors should be clearly identified with new and prospective clinical studies.

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