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# Cisplatin-based chemotherapy in elderly patients with advanced stage (IIIB and IV) non-small cell lung cancer patients

S. OZKAYA[1], S.FINDIK[2], A. G. ATICI[2] A. DIRICAN[3]

*[1]Rize University, Faculty of Medicine, Department of Pulmonary Medicine, Rize, Turkey,e-mail: ozkayasevket@yahoo.com , [2]Ondokuz Mayis University, Faculty of Medicine, Department of Pulmonary Medicine, Atakum, Samsun, Turkey, [3]Medicalpark Hospital, Department of Pulmonary Medicine, Atakum, Samsun, Turkey*

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Lung cancer continues to be the leading cause of cancer-related mortality and approximately 70% of patients present with locally advanced or metastatic disease at the time of diagnosis. More than 50% of lung cancer cases are diagnosed in patients over the age of 65 years. The doublet chemotherapies consisting of platinum plus one of the third-generation agents become currently the standard regimen, the first line chemotherapy The most of the available data regarding the optimal treatment of lung cancer comes from clinical trials in which the vast majority of patients are significantly younger than 65 years of age.

We aimed to investigate whether there is any difference in tolerability and efficacy in between adult(<65 years old) and elderly(≥65 years old) patients who received cisplatin based chemoteherapy or chemoradiotherapy for stage IIIB and IV non-small cell lun cancer.

We retrospectively evaluated the total 134 patients with advanced stage (stage IIIB or IV) NSCLC, in Ondokuzmayıs University, Faculty of Medicine, Department of Pulmonary Medicine between 2001 and 2004.

The response rates were 30.3% in adults and 28.8% in elderly patients. The median survival was 13.6±1.4 months and 11.8±2.0 months for adults and elderly patients, respectively. The one-year, two year and five year survival rates were 37%, 9% , 4% for adult patients and 29%, 7%, 4% for elderly patients, respectively. There was no statistical difference between the groups. Percentages of grade 3-4 anemia (0% vs 6.6%) and grade 3-4 neutropenia (0% vs 4.4%) were higher in elderly patients than adult patients. Other toxic effects were similar among both of groups.

In conclussion; standart cisplatin containing chemotherapy regimens (cisplatin plus gemcitabine or vinorelbine) can be used in elderly patients with advanced non-small cell lung cancer.

*Key words: Non-small cell lung cancer, chemotherapy, cisplatin, elderly*

Lung cancer continues to be the leading cause of cancer-related mortality and approximately 70% of patients are alrady present with locally advanced or metastatic disease at the time of diagnosis. More than 50% of lung cancer cases are diagnosed in patients over the age of 65 years [1]. Patients with resectable disease may be cured by surgery or surgery with adjuvant or neoadjuvant therapy. Since surgery is not curative for the advanced stages (IIIB and IV) non-small cell lung cancer (NSCLC), chemotherapy and/or radiotherapy are the reference treatments. Over past decade, third generation agents such as vinorelbine, taxanes, and gemcitabine have been introduced to treatment of NSCLC [1]. Combination of one or more of these agents with a platinum compound has resulted in high response rates and prolonged overall survival. Today, doublet chemotherapies consisting of platinum plus one of the third-generation agents become currently the standard regimen, the first line chemotherapy [2]. The most of the available data regarding the optimal treatment of lung cancer comes from clinical trials in which the vast majority of patients are significantly younger than 65 years of age. The cisplatin based chemotherapy is not prefered in elderly patient with advanced non-small cell lung cancer and there are no enough data on the effectiveness of cisplatin based chemotherapy in elderly patients (3). We aimed to investigate whether there is any differences in tolerability and efficacy in between adult(<65 years old) and elderly(≥65 years old) patients who received cisplatin based chemoteherapy or chemoradiotherapy in patients with stage IIIB and IV NSCLC.

## Material and methods

We identified consecutive 134 patients with advanced stage (stage IIIB or IV) NSCLC, in Ondokuzmayıs University,

Faculty of Medicine, Department of Pulmonary Medicine, between 2001 and 2004. Data including demographic values, medical histories, symptoms and signs, laboratory examination results, and radiologic and scintigraphic documents were taken from files of the patients and archives of the department, respectively. Performance status was classified in accordance with the criteria of European Cooperative Oncology Group (ECOG). Staging was conducted by evaluation of the imaging methods, chest x-ray, thoracic computed tomography, abdominal computed tomography, abdominal ultrasonography (USG), cranial computed tomography and bone scintigraphy .The criteria for eligibility included pathologically confirmed NSCLC, radiologically measurable lesion; an age of at least 18 years; adequate hematologic function (as indicated by a white-cell count of at least 4.000 per cubic millimeter and a platelet count of at least 100.000 per cubic millimeter), hepatic function (as indicated by a billirubin level that did not exceed 1.5 mg per decilitre, and AST and ALT levels being less than three times of the normal values), and renal function (as indicated by a creatinine level that did not exceed 1.5 mg per deciliter); and ECOG performance status of ≤ 2. Criteria as to the exclusion from the study were as follows: insufficient hematological, renal and hepatic functions; probability of brain metastasis; history of prior chemotherapy and/or radiotherapy; presence of uncontrolled infections; presence of an additional malignancy; presence of a systemic disease contradicting administration of chemotherapy; pregnancy; performance status of >3; unfitness for follow-up due to psychological, familial, sociological and geographical reasons. The main treatment was chemotherapy for patients with stage IV disease and sequential chemoradiotherapy for patients with stage IIIB disease. Vinorelbine, at a dose of 30 mg per square meter or Gemcitabine, at a dose of 1250 mg per square meter were administered on days 1, and 8, and cisplatin, at a dose of 80 mg per square meter on day 1 of a three-week cycle. The cycle was repeated every three weeks. At least two cycles were given to the patients were considered assessable for response. Patients who responded to the treatment and did not show signs of toxicity or progression were given four to six cycles. Dosage was adjusted according to hematological, neurological, renal and hepatic functions. Dosage was decreased by 25% for patients who were classified as Grade III or Grade IV in accordance with WHO toxicity criteria. Curative radiotherapy was administered tgo all patients with stage IIIB disease who had responded to chemotherapy after three cycles of chemotherapy regimens. And remaining one to three cycles were given after three weeks to one-month after administration of radiotherapy.

The aim of this nonrandomized comparison of retrospective study was to evaluate the activity (response rates, 1-,2- and 5-years survival and overall survival) and toxicity of cisplatin-plus-third generation cytotoxics (vinorelbine or gemcitabine) regimens in elderly (≥65 years old) and adult (<65 years old) patients with stage IIIB or IV non-small cell lung cancer. Standard ECOG response criteria were used. The response was evaluated by thorax CT scan at after two cycles of chemotherapy and end of the treatment. Briefly, a complete response was defined as the absence of disease at all known sites for at least four weeks. A partial response was defined as a 50 percent reduction in the sum of the perpendicular diameters of all measurable lesions, lasting at least four weeks. Progressive disease was defined as either a 25 percent increase in the area of any one lesion over the prior measurement or the development of one or more new lesions. Survival was calculated from the date of diagnosis to the date of death or the date when the patient last known to be alive.

All patients gave written informed consent.

**Statistical analysis.** Data was evaluated by using SPSS 13.0 programme (SPSS Inc., Chicago, IL, USA). Survival of the patients was calculated from the date of diagnosis to the date of death. Response rates were calculated for patients with complete or partial responses. Median age, smoking habits, performance status, response rates and toxicity results of the groups were compared by using "Mann-Whitney U" and "Pearson chi-square" tests. Median survival and 5 year survival rates of the groups were calculated by Kaplan–Meier method. Median survival rates were compared by using log-rank test. In all tests, p value was considered to be significant when it was 0.05 or less.

## Results

A total of 134 patients, 89 patients for the adults (<65 years old) group and 45 patients for the elderly (≥65 years old) group were enrolled in the study between January 2001 and September 2004. The baseline characteristics of the patients are shown in Table I. The most of patients in elderly group had ECOG 2

**Table 1. Baseline characteristics of the patients**

| | ADULT (<65 YEARS OLD) (n=89) | ELDERLY (≥65 YEARS OLD) (n=45) |
|---|---|---|
| CHARACTERISTIC | | |
| Age (mean-year) | 54.2±7.5 | 69.5±3.2 |
| Sex (% of patients) | | |
| Female 9 8 | | |
| Male 91 92 | | |
| Smoking Status (% of patients) | | |
| Nonsmoker | 4.4 | 4.4 |
| <10 pack/year | 3.3 | 4.4 |
| 10-20 pack/year | 11.2 | 2.2 |
| 21-30 pack/year | 23.5 | 17.7 |
| >30 pack/year | 57.3 | 71.1 |
| Performance status (% of patients)* | | |
| 0 | 6.7 | 2.2 |
| 1 | 50.5 | 28.8 |
| 2 | 42.7 | 68.8 |
| Disease stage (% of patients) | | |
| IIIB | 68.5 | 53.3 |
| IV | 31.5 | 46.7 |
| Histological Type (% of patients) | | |
| Squamous cell | 69.7 | 69 |
| Adenocarcinoma | 16.8 | 22.2 |
| Undifferentiated NSCLC | 13.5 | 8.8 |

*Pearson chi-square test, p<0.05

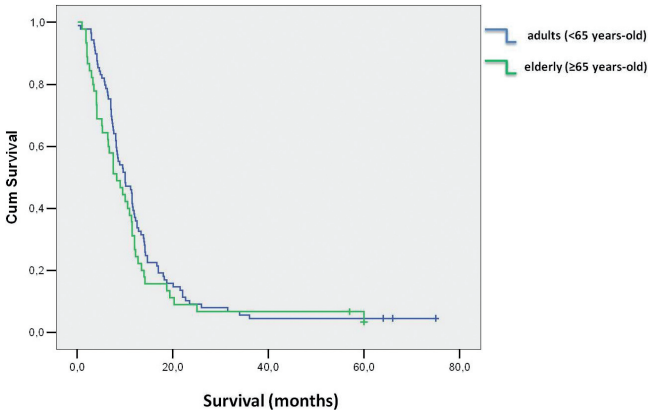


**Figure 1 The cumulative survival graphics of adults and elderly patients are showing in Kaplan-Meier suvival curves.**

performance status and it was higher than adults. There was no statistical difference between the groups with respect to other baseline clinical characteristics of the patients. The median number of chemotherapy cycles were 3.6 for patients in adult group and 3.7 in elderly group.

Table 2 presents outcome results of the treatment groups. There were no significant differences in the response rate or survival among the groups. The response rates were 30.3 percent for adult patients and 28.8 percent for elderly patient. The median survival was 13.6±1.4 months for the adult group, 11.8±2.0 months for elderly group. The one-year, two year and five year survival rates were 37%, 9% and 4% in adult group, 29%, 7% and 4% in elderly group, respectively (Table II and Figure 1).

Table 3 shows toxic effects of the treatment groups. No treatment-related death was observed and no patient was withdrawn from the study due to toxicity. The major hematological toxicities encountered in this study were neutropenia, febrile neutropenia, thrombocytopenia and anemia. Percentages of grade 3-4 anemia (0% vs 6.6%) and grade 3-4 neutropenia (0% vs 4.4%) were higher in elderly group than adult group. There was no statistical difference between the groups with respect to other toxicity in the patients. Febrile neutropenia was seen in 5 patients (2.2%) among adult group and in 2 patient (4.4%) among elderly group and this difference was not statistically significant. The thrombocytopenia occurred in 15.7% of patients among adult group and in 24.3% of patients among elderly group, the difference was not statistically significant. No serious hemorrhagic events were noted on either regimens.

Non-hematological toxicity was minimal. The nausea and vomiting were observed in 63.9% of patients in adult group and in 75.4% of patients in elderly group. And the difference was not statistically significant.

## Discussion

Every year, 1.2 million new cases of lung cancer are diagnosed worldwide and lung cancer is the leading cause of cancer death in most developed nations (4). More than 50% of lung cancer cases are diagnosed in patients over the age of 65 years. Age affects the choice of treatment regimens for patients with non-small cell lung cancer [1]. Recent reports indicate that just over 20% of elderly patients with advanced lung cancer ever receive chemotherapy [5]. The cisplatin-based chemotherapy was the only choice of treatment for advanced NSCLC (2). According to reported articles, the cisplatin is particularly difficult to use in elderly patients because of renal and neurological side effects and potential hydration-related problems [1,6]. Most elderly patients with advanced NSCLC don't receive any chemotherapy, and those who do usually receive only single-agent therapy. Few prospective clinical experiences with cisplatin-based chemotherapy in elderly patients with NSCLC have been reported. In some retrospective analyses of large randomized trials with cisplatin or carboplatin-based

**Table 2. Outcomes of treatment groups**

| | ADULT (<65 YEARS OLD) | ELDERLY (≥65 YEARS OLD) | *p* |
|---|---|---|---|
| VARIABLE (N=89) | (N=45) | | |
| Response-% | | | |
| Complete response | 3.3 | 4.4 | |
| Partial response | 41.4 | 42 | |
| Stable disease | 40.7 | 42 | |
| Progressive disease | 14.6 | 11.6 | |
| Overall response rate-% | 30.3 | 28.8 | *0.73** |
| Survival | | | |
| Median (95% CI)-mo | 13.6±1.4 | 11.8± 2.0 | *0.48*** |
| One- year survival- % | 37 | 29 | |
| Two- year survival- % | 9 | 7 | |
| Five- year survival- % | 4 | 4 | |

*Pearson chi-square test.
** Log-Rank Test.

**Table 3. Toxic effects**

| TYPE OF TOXIC EFFECT | ADULT (<65 YEARS OLD) (n=89) | ELDERLY (≥65 YEARS OLD) (n=45) |
|---|---|---|
| | % of patients | |
| Anemia | | |
| Grade 1-2 | 39.3 | 46.6 |
| Grade 3-4* | 0 | 6.6 |
| Neutropenia | | |
| Grade 1-2 | 29.2 | 24.4 |
| Grade 3-4* | 0 | 4.4 |
| Febrile neutropenia | 2.2 | 4.4 |
| Thrombocytopenia | | |
| Grade 1-2 | 10.1 | 15.5 |
| Grade 3-4 | 5.6 | 8.8 |
| Nausea and vomiting | | |
| Grade 1-2 | 61.7 | 68.8 |
| Grade 3-4 | 2.2 | 6.6 |

*Pearson chi-square test, p< 0.05

chemotherapy in patients with advanced NSCLC found no differences in survival between elderly and younger patients, with small increase in toxicity in the elderly, and suggest that advanced age alone should not preclude platin-based chemotherapy for NSCLC, as in our study [7-11].

We found that the response rates were 30.3% for adult patients and 28.8% for elderly patients. The median survival was 13.6±1.4 months in adult group, 11.8±2.0 months in elderly group. The one-year, two year and five year survival rates were 37%, 9% and 4% for the adult group, 29%, 7% and 4% for the elderly group, respectively (Table @ and Figure 1). There was no statistical difference between the groups.

Langer et al, reported that the leukopenia was significantly more common in elderly than in younger patients. The objective response rates (21.5% vs 23.3%), median survival times (9.05 vs 8.53 months) and 1 year survival rates (38% vs 29%) were similar in younger and older groups, respectively [7]. This result was consistent with our results. Also, anemia was significantly more common in elderly than in younger patients. Other toxic effects were similar betwwen elder and younger patients. Kelly et al. found that the grade 3-5 toxicities, both hematological and non-hematological, were similar between the two age groups,that is, those older and those younger patients, altough there was a trend toward more toxicity in the older group with drug combination. There was also a trend toward shorter median survival in the older group (8.6 vs 6.9 months) and the survival rate was somewhat higher in the younger group (40% vs 30%) [9]. The previously repoted articles suggest that concurrent chemotherapy plus radiotherapy is both tolerable and beneficial in elderly patients with stage III non-small cell lung cancer who are in good overall physical condition [12].

Patients with a limited performance status have a shorter survival time and are much less likely to benefit from treatment. The particular type of treatment recommended for an individual patient is dependant on his or her performance status, degree of prior weight loss, and overall medical condition. Chemotherapy is an appropriate intervention for elderly patients with advanced NSCLC with good performance statuses (ECOG 0-2) [13].

In conclussion, the age alone should not preclude platin-based chemotherapy for NSCLC. Standart cisplatin-based chemotherapy regimens should be used in elderly patients with a good performance status for treatment of advanced non-small cell lung cancer.

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