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Research Article

Effect of Smoking Status on Hematological Toxicities and Effectiveness of First-line Platinum-based Chemotherapy Administered to Patients with Non-small-cell Lung Cancer

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Abstract

Objectives: In this paper we thus aimed to determine whether smoking during chemotherapy affects the outcome of non-small cell lung cancer (NSCLC) treatment and increases hematological side effects.

Methods: We have reviewed 70 stage-IV NCSLC patients, who had received chemotherapy as the firstline therapy. Smoking status before and during the administration of the firstline therapy, therapeutic regimens, clinical outcomes, hematological adverse events, and infections that develop during the chemotherapy were investigated.

Results: 26 (37.1%) of the patients were former smokers, 44 (62.9%) of the patients were current smokers. 13 (18.6%) patients quit smoking <1 year before, 11 (15.7%) of them stopped smoking <2 weeks before the treatment. 20 (28.6%) of the patients continued to smoke actively during the therapy. No significant differences were found between the smoking groups in terms of neutropenia, anemia, infections that develop during the chemotherapy (p=0.259, p=0.158, p=0.342, respectively). Significant differences were found between the smoking groups in terms of thrombocytopenia and smoking pack-years (p=0.007, p=0.008, respectively).

Conclusion: This is the first study evaluating smoking status on hematological toxicities in NSCLC. It should be emphasized however that this study was limited mainly to the patients with stage-IV NSCLC patients, who received palliative treatment.

Keywords: Hematological toxicities, lung cancer, smoking status

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Lung cancer is the world's leading cause of cancer-related deaths. Smoking constitutes the major risk factor for lung cancer in approximately 87% of patients.[1] Although it is well known that lung cancer is linked to tobacco use, molecular analyses over the last decade have shown that driver mutations are more common in never-smokers than heavy smokers.[2] The kind of consequences caused by continuing to smoke after having been diagnosed with cancer has always been a matter of concern and has been addressed in many studies. In this study, we aimed to de-

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termine whether smoking during chemotherapy affects the outcome of non-small cell lung cancer (NSCLC) treatment and increases hematological side effects, such as neutropenia, anemia, and thyrombocytopenia.

Methods

We have searched the database of the Department of Medical Oncology in Istanbul University-Cerrahpasa Cerrahpasa Medical Faculty between January 2016 and December 2019. We have obtained the approval of the local ethics committee to conduct a human investigation, and conducted this study retrospectively in accordance with the ethical principles set forth by the Declaration of Helsinki. We have reviewed the patients' records, and determined as a result their the demographics, smoking status before and during firstline therapy, the disease stage (according to the AJCC staging system), performance status (Eastern Cooperative Oncology Group scale [ECOG]),[3] cancer histology subtype, number of metastatic sites, therapeutic regimen, duration of treatment, treatment response, clinical outcome, progression-free survival (PFS), hematological adverse events affected the treatment (neutropenia, anemia, and thrombositopenia) and infections that develop during the first-line treatment before first progression period. The eligibility criteria were; being aged >18 years, a diagnosis of stage IV NSCLC, having received no prior therapy, having received a negative EGFR, ALK, ROS, BRAF test result, and having been receiving chemotherapy as the first-line therapy. All patients received platinum based chemotherapy. Patients were categorized according to the criteria set forth by the ECOG performance status. Patients, who received 0 and 1 as the ECOG performance status of were deemed to be eligible for the study. Patients, who had previously smoked >100 cigarettes in his/her lifetime were included in the study. Smoking history was calculated based on the patients' self-reports as reported by the attending physician. Smoking data included the number of pack-years smoked (i.e., the average number of cigarette packs smoked per day multiplied by the number of years smoked); and the smoking status (former smoker or current smoker. A former-smoker was described as a patient who had smoked >100 cigarettes in his/her lifetime and had quit smoking >1 year before diagnosed. Current smokers were divided into three subgroups; the continuous subgroup comprised of patients, who continued to smoke actively during the therapy; the quit subgroup comprised of patients, who quit smoking <1 year before the treatment (c-quit); and the stopped subgroup comprised of patients, who stopped smoking within 2 weeks before the treatment (c-stopped). The patients included in the study were the ones that received first-cycle chemotherapy, whereas the patients, who received immunotherapy or targeted therapy were excluded from the study. All toxicities to chemotherapy were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0.[4] Responses to treatment were categorized per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria[5] and were reported as best response. Overall survival (OS) is calculated from the time of metastatic diagnosis to the death or the last visit date if the patient is alive. Progression-free survival (PFS) is defined as the time from the first-line treatment start time to disease progression time.

Statistical Analysis

Commercial software (SPSS version 16.0®, SPSS, Chicago IL, USA) was used for the statistical analysis. Standard descriptive statistics were used to summarize all variables. The Kolmogorov–Smirnov test was used to analyse the normal distribution of data. The distribution of continuous variables between smoking groups was assessed by the KruskalWallis test as they were not normally distributed. Chi-square test was used for categorical variables. Kaplan-Meier plots were used to analyse survival data. Multivariate analysis was done using cox reggression. P values <0.05 were accepted as statistically significant.

Results

A total of 70 patients those met the selection criteria were included in the study. The median follow up duration of the study was 4 years. All patients recieved first-line platinum based chemotherapy. The median age of the patients at the time of the diagnosis of metastatic lung cancer was 63. All patients were stage IV lung cancer. 66 (94.3%) of the patients were male, and only 4 (5.7%) of the patients were female. The demographic and clinical characteristics of these patients are shown in Table 1. 35 (50%) patients received palliative radiotherapy (RT) and 16 of these patients received RT on brain. 26 patients (37.1%) were former smokers, 44 patients (62.9%) were current smokers. Current smokers were divided into 3 subgroups; 20 (28.6%) of the patients continued to smoke actively during therapy, 13 (18.6%) of the patients quit <1 year before the treatment, and 11 (15.7%) of the patients stopped <2 weeks before the treatment. Mean number of cigarettes smoked by the 20 patients, who were continous smokers, were 12.25 pieces per patient. We have investigated the relationship between the smoking status, the side effects (neutropenia, thrombocytopenia, anemia) caused by the treatment, and the infection status (Table 2). There were no significant differences between smoking groups in terms of neutropenia, anemia, infections that develop during the chemotherapy, site metastasis and age (p=0.259, p=0.158,

Table 1. Patient demographic and clinical characteristics

Characteristics (n=70)	Values (%)
Age,median	63
Sex	
Men	66 (94.3)
Women	4 (5.7)
ECOG PS	
0	15 (21.4)
1	51 (72.9)
2	4 (5.7)
Histology	
Adenocarcinoma	42 (60)
Squamous cell	19 (27.1)
Other	9 (12.9)
Smoking Status	
Former	26 (37.1)
Quit<1 year	13 (18.6)
Stopped<2 weeks	11 (15.7)
Continuous	20 (28.6)
Smoking History, pack-year,mean	48.5
Radiotherapy (Paliative)	
Yes	35(50)
No	35(50)
Site Metastasis	
Single	28 (40)
Multiple	42 (60)
Liver Metastasis	
Yes	15 (21.4)
No	55 (78.6)
Brain Metastasis	
Yes	19 (27.1)
No	51 (72.9)
Bone Metastasis	
Yes	35 (50)
No	35 (50)
Surrenal Metastasis	
Yes	21 (30)
No	49 (70)

ECOG PS: Eastern Cooperative Oncology Group Permormance Status.

p=0.342, p=0.192, respectively). Neutropenia was observed in 30 (42.8%) of the patients. 2 of these patients had grade-4 neutropenia, 8 patients had grade-3 neutropenia, 14 patients had grade-2 neutropenia, and 6 patients had grade-1 neutropenia. Anemia was observed in 35 (50%) of the patients. 1 patient had grade-4 anemia, 9 patients had grade-3 anemia, 12 patients had grade-2 anemia, and 13 patients had grade-1 anemia. Infection was observed in 33 patients. 2 of these patients had urinary tract infection, 1 of them had gastroenteritis, and the remaining patients with infection had a lung infection. There were significant differences between smoking groups in terms of thrombocytopenia and smoking pack-years (p=0.007, p=0.008, respectively). In post-hoc analysis when compared in terms of thrombocytopenia, a statistically significant difference was observed between those who quit within 1 year and the other groups (p<0.05). Thrombocytopenia was observed in 28 (40%) patients. 2 of these patients had grade-3 thrombocytopenia, another 2 patients had grade-2 thrombocytopenia, and the the remaining patients with thrombocytopenia had grade-1 thrombocytopenia. We did not investigate whether there was a difference between the smoking groups on the basis of gender as we had only 4 female patients compared to 66 male patients.

51 (72.8%) patients received cisplatin based chemotherapy and 19 (27.2%) patients received carboplatin based chemotherapy. In 7 patients, maintenance chemotherapy followed first-line chemotherapy. We categorized the patients on the basis of the type of the chemotherapy they received, that is either carboplatin or cisplatin based chemoterapy, and found no differences between these two categories in terms of neutropenia, anemia and thrombocytopenia (p=0.366, p=0.141, p=0.27 respectively). We have found the overall response rate (ORR: complete response (CR)+partial responses (PR)) to first line platinum-based chemotherapy as %28.57. One patient experienced CR and 19 patients experienced PR. OS and PFS ratios found as a result of the Kaplan-Meier survival analyses of the smoking groups are presented in Table 3. The median OS for all patients was found to be 14.86 ±2.4 months. The median PFS for all patients was found to be 4.16±1.0 months. There was no significant difference between the smoking groups in terms of OS (Fig. 1) and PFS (Fig. 2) (p=0.24, p=0.537, respectively). Multivariate analyzes using cox reggression are summarized in Table 4. For overall survival infection under chemotherapy, bone, brain, liver metastasis, histology and ECOG PS were independent predictors of early mortality.

Discussion

There is a growing body of literature on the adverse effect of smoking on the treatment outcomes in patients with NSCLC. Effect of smoking after having been diagnosed with lung cancer has always been an intriguing topic. Although it has been suggested in some studies that smoking is an indicator of poor prognosis,[6] there are other studies where no such association was found.[7] In one of these studies, smoking was found to be a negative prognostic factor for only males,[8] whereas in another study, it was found to be a negative prognostic factor for only females.[9] Thus, the current literature is controversial in this sense. This study on the other hand, to the best of our knowledge, is the first study to date, in which the effect of smoking on hemato-

Table 2. Relationship between smoking status and patients' characteristics

	Former smokers	Smokers quit smoking <1 year ago	Smokers stopped smoking <2 weeks ago	Continuous smokers	p
Age (Median)	65 (48-82)	62 (48-78)	62 (42-72)	61.5 (44-80)	0.192[a]
Pack Years (Median)	30 (5-120)	50 (20-96)	40 (30-100)	50 (35-200)	0.008[a]
Neutropenia, n (%)					
Yes	10 (38.5)	8 (61.5)	6 (54.5)	6 (30.0)	0.259[b]
No	16 (61.5)	5 (38.5)	5 (45.5)	14 (70)	
Thrombocytopenia, n (%)					
Yes	7 (26.9)	10 (76.9)	6 (54.5)	5 (25.0)	0.007[b]
No	19 (73.1)	3 (23.1)	5 (45.5)	15 (75.0)	
Anemia, n (%)					
Yes	9 (34.6)	9 (69.2)	7 (63.6)	10 (50)	0.158[b]
No	17 (65.4)	4 (30.8)	4 (36.4)	10 (50)	
Infections that developed during chemotherapy, n (%)					
Yes	8 (30.8)	6 (46.2)	6 (54.5)	11 (55.0)	0.342[b]
No	18 (69.2)	7 (53.8)	5 (45.5)	9 (45.0)	
Site Metastasis, n (%)					
Single Metastasis	13 (50.0)	4 (30.8)	4 (36.4)	7 (35.0)	0.612[b]
Multiple Metastases	13 (50.0)	9 (69.2)	7 (63.6)	13 (65.0)	

[a]: P-values for Kruskal—Wallis tests; [b]: P-values for chi-square tests.

Table 3. The Kaplan-Meier survival analyses of smoking groups in respect of OS and PFS

	n	Median OS (months±S.E.)	95% C.I.	p	Median PFS (months±S.E.)	95% C.I.	p
Former smokers	26	16.8±2.8	11.2-22.3	0.24	5.1±2.0	1.1-9.09	0.537
Quit <1 year ago	13	12.1±3.7	4.7-19.6		5.2±1.3	2.6-7.8	
Stopped <2 weeks ago	11	7.3±0.7	5.9-8.7		2.9±0.07	2.7-3.07	
Continuous smokers	20	21.4±8.6	4.3-38.4		4.1±0.8	2.5-5.7	

OS: Overall survival; PFS: Progression-free survival; C.I.: 95% confidence interval; S.E.: Standard error.

logical toxicities of platinum based chemotherapy, was studied.

There are several studies about the effect of smoking on the side effects of cancer treatment. Luke J. Peppone et al.[10] studied the effect of smoking on side effects of cancer treatment, such as hair loss, weight loss, skin problems, depression, sleep problems, pain, and fatigue. They found that the toxicity levels induced by the cancer treatment on the patients that have continued to smoke during the cancer treatment were higher than the patients that did not smoke. Sevin Baser et al.[11] tried to find an answer to the question of whether quitting smoking after having been diagnosed with lung cancer is associated with the performance status or not, and they have found as a result of their study that the patients who continued to smoke after having been diagnosed with lung cancer had a worsening performence status. However, hematological side effects of smoking was not addressed in that study. On the other hand, no significant differences were found in this study between the smoking groups in terms of neutropenia and anemia following the administration of first-line platinum chemotherapy on metastatic lung cancer patients. The fact that the patients continued to smoke or quit smoking after having been diagnosed with lung cancer did not seem to make any difference in terms of anemia, neutropenia and developing an infection. Regardless, the effect of smoking on the quantity of platelets was found to be still controversial, as it might be another contributing factor. Smoking has a major role in disrupting the platelet count, activation and aggregation.[12] It was revealed by this study that there were statistically significant differences between the smoking groups in terms of thrombocytopenia. Smoking was found to have considerable effects on the increase of mean platelet count in the healthy males. Anandhalaksh-

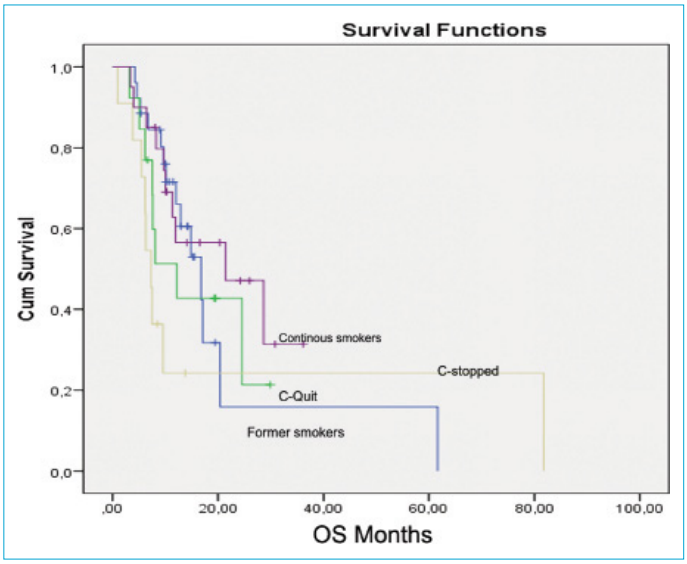

Figure 1. There was no significant difference between the smoking groups in terms of OS (p=0.24).

OS: Overall survival.

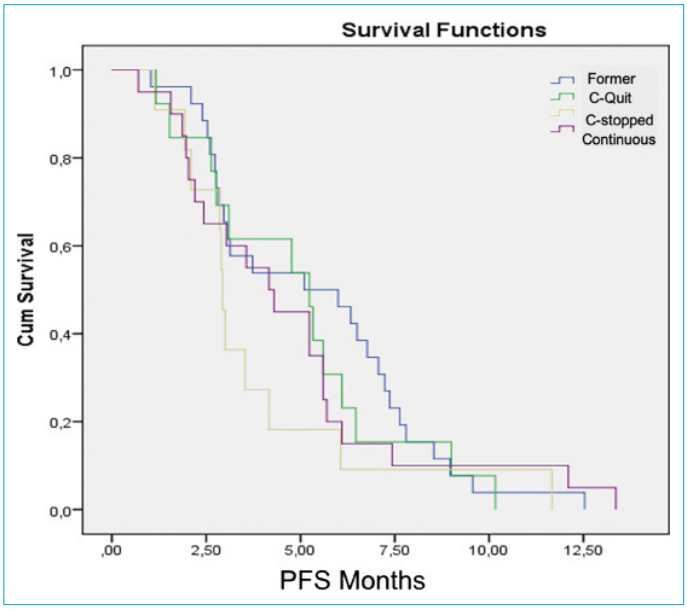

Figure 2. There was no significant difference between the smoking groups in terms of PFS (p=0.537).

PFS: Progression-free survival.

mi Swaminathan and his friends[13] showed that cigarette smoking in healthy men was accompanied by significant effects on platelet indices in comparison with nonsmokers. Chao et al.[14] also reported a significant increase in the platelet counts of smokers. In addition, Hirohiko Morita et al.[15] reported in their study that only two weeks of smoking cessation can improve the enhanced platelet aggregability and intraplatelet redox imbalance in long-term smokers, possibly by decreasing oxidative stress, in our study a

Table 4. Multivariate Analysis using Cox regression method

Variables	Overall survival		
	Relative risk	95% C.I.[a]	p[b]
Infection under chemotherapy	3.90	(1.94-7.87)	0.00
Brain Metastasis	4.75	(2.24-10.04)	0.00
Bone Metastasis	2.70	(1.29-5.64)	0.008
Liver Metastasis	3.49	(1.41-8.61)	0.007
Histology	2.64	(1.42-4.93)	0.002
ECOG PS	2.42	(1.04-5.62)	0.039

ECOG PS: Eastern Cooperative Oncology Group Permormance Status. [a]: 95% Confidence interval; [b]: P valuse of Cox regression analysis.

statistically significant difference was observed between those who quit within 1 year and the other groups. However, we cannot attribute much clinical significance to this thought, as the number of patient numbers reviewed within the scope of our study was low.

We did not find any statistically significant difference between the OS and PFS rates of different smoking groups. It should be noted however that we have only included stage IV lung cancer patients in our study, and excluded never-smokers. There are many studies about the effects of smoking on the outcome of the lung cancer treatments. A significant difference between the OS rates of different smoking groups, that is, of the current smokers, non-smokers or smokers that quit >2 years those have stage I/II NSCLC, has been revealed in Jana L. Fox et al.'s[16] study. However no significant difference was found in the same study between the OS rates of the said smoking groups those have stage III NSCLC. Again, in another study, in which early-stage lung cancer was studied, Peyman Sardari Nia et al.[17] found that non-smokers, former smokers and recent quitters had a significantly better prognosis compared to the current smokers. It was found as a result of a study conducted on 4200 patients that former smokers or never-smokers with stage-IV lung cancer had no survival benefit with the increase in their age, which in fact might be the reason why we did not find any difference among the smoking groups as a result of the survival analysis, since the mean age of the patients included in our study was 63.[18] It was suggested as a result of a large-scale study conducted on 4546 patients that smoking status was not an important determinant of overall survival rate in NSCLC patients. In this study, Meguid et al.[19] compared current smokers versus never smokers with respect to mortality and observed no difference in survival. Similarly, Toh et al.[7] did not find any difference between current smokers and never smokers in terms of survival as a result of their study they conducted on 317 patients from Singapore. In comparison, we, as well, did not find any dif-

ference between the smoking groups in terms of survival.

Furthermore, we have found that carboplatin or cisplatin based chemotherapy did not yield any difference in terms of hematological toxicity, which supported the results reported by Eun Ji Nam et al.[20]

However, there are some limitations of our study. First of all, it is a retrospective study, secondly it is a monocentric study, and thirdly the number of patients those have been reviewed within the scope of the study is low. The fact that a limited number of patients was reviewed within the scope of the study prevented us from making conclusive conclusions. In addition, we did not have any subsequently measured biochemical evidence, such as the expired carbon monoxide or serum nicotine levels of patients, which could have been used to support the responses provided by the patients to our question about smoking that were based solely on patients' self-reports.

In conclusion, this has been the first study to date, in which the effect of smoking on the hematological toxicities of platinum based chemotherapy administered to patients with NSCLC, was studied. As a result of the study, we have not found any difference between the smoking groups in terms of anemia, neutropenia and infection, other than thrombocytopenia. We also have not found any difference between the smoking groups in terms of OS and PFS. It should emphasized however that this study was limited mainly to the patients with stage IV NSCLC, who received palliative treatment. Prospective studies with larger samples are needed to be carried out to further clarify this important issue.

Disclosures

Ethics Committee Approval: Istanbul University-Cerrahpasa Cerrahpasa Faculty of Medicine, 07/08/2019 and 121232 number.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – N.S.S.; Design – N.S.S., E.C.; Supervision – N.S.S., E.C.; Materials – N.S.S., E.D.; Data collection or processing – O.E.T., E.D.; Analysis or interpretation – N.S.S., F.H.D., E.C., N.S.D.; Literature search – N.S.S.; Writing – N.S.S.; Critical review – F.H.D., N.S.D., N.S.S.

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