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Smoking cessation before initiation of chemotherapy in metastatic non-small cell lung cancer: influence on prognosis

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TO THE EDITOR:

Cigarette smoking is the most established risk factor for lung cancer (LC), and approximately 70% of LC-related deaths are attributable to tobacco.[1] Carcinogens in tobacco smoke may not only act as genetic inducers but also act as promoters of disease progression.[2] In addition, smoking has various other negative effects, such as decreased quality of life[3] and worsening of performance status[4] in patients that continue to smoke after LC diagnosis. Previous data have shown that continued smoking after a diagnosis of early-stage LC is associated with higher risk of LC recurrence, second primary tumor, and all-cause mortality.[5] The impact of smoking cessation during treatment on outcomes in patients with metastatic disease is not well defined. Herein, our objective was to evaluate the impact of smoking cessation prior to the initiation of chemotherapy on overall survival (OS) on patients with advanced non-small cell lung cancer (NSCLC).

Between January of 2011 and December of 2015, patients referred to our center and diagnosed with metastatic adenocarcinoma or squamous cell carcinoma (SCC) were retrospectively studied. Patients with active smoking habits and treated with at least one cycle of chemotherapy were included; patients treated with tyrosine kinase inhibitors were excluded. The systemic therapy was never delayed regardless of the smoking status of the patients. All patients included in the study were submitted to a brief intervention for smoking cessation and were invited to participate in a specialized consultation. Smoking cessation was confirmed by exhaled CO measurements. We compared the clinical characteristics of the patients who achieved smoking cessation with those who did not. These two groups were further subdivided according to histological results in order to investigate OS, which was defined as the time interval between the pathological diagnosis and death or last follow-up evaluation. Survival estimates were obtained using the Kaplan-Meier method. Cox regression was used to test the impact of multiple variables on OS.

The study comprised a total of 97 patients (mean age = 57 ± 10 years), 89 of whom were male (91.8%). The main histological type was adenocarcinoma, in 74 patients (76.3%); 52 patients (53.6%) were classified as having an Eastern Cooperative Oncology Group performance status scale[6] score of 1; and 55 (56.7%) showed no weight loss at diagnosis. The most prevalent comorbidities were arterial hypertension, in 18 patients (18.6%); and diabetes mellitus (DM), in 7 (7.2%). Of the 97 patients, 79 (81.4%) had a smoking history > 30 pack-years. The chemotherapy regimens used were platinum combined with pemetrexed, in 67 patients (39.1%); platinum combined with gemcitabine, in 17 (17.5%); and monotherapy with oral vinorelbine, in 13 (13.4%). Smoking cessation occurred in 50 patients (51.5%), but it only occurred after the initiation of chemotherapy in 47 (48.5%), and only 11 (22%) participated in a specialized consultation. The median time of smoking cessation was 4 months (interquartile range: 12.2). The comparison of these two subgroups regarding the characteristics studied showed no significant differences except for gender (Table 1). The subgroup of patients who quit smoking prior to chemotherapy initiation, when compared with those who continued to smoke during chemotherapy, showed a higher median OS in general. However, this difference was significant in those diagnosed with SCC (7.0 months vs. 2.5 months; p = 0.010), but not in those with adenocarcinoma (10 months vs. 9 months; p = 0.754; Figure 1). The multivariate analysis showed that smoking cessation prior to chemotherapy was the only factor associated to longer OS—hazard ratio (HR) = 0.19; p = 0.004; 95% CI: 0.06-0.59—in SCC patients. In patients with adenocarcinoma, the multivariate analysis showed a poorer prognosis in those treated with carboplatin plus pemetrexed (HR = 2.29; p = 0.003; 95% CI: 1.32-3.40) or monotherapy with oral vinorelbine (HR = 3.46; p = 0.002; 95% CI: 1.57-7.63) when compared with patients treated with cisplatin plus pemetrexed. The presence of DM was associated with a protective effect (HR = 0.27; p = 0.029; 95% CI: 0.08-0.87), as well as the total time of smoking cessation, with a decrease of approximately 8% in the risk of death for each month of smoking cessation (HR = 0.92; p < 0.001; 95% CI: 0.90-0.95).

Smoking has been described as an independent prognostic factor for poor survival in patients with advanced NSCLC.[7] However, the impact of smoking cessation on metastatic LC prognosis prior to the initiation of chemotherapy was not evaluated. Our retrospective review of a five-year experience in managing the two most common types of NSCLC has shown that continued tobacco use by SCC patients during chemotherapy is associated with decreased survival. We also found a similar tendency in patients with adenocarcinoma. The difference regarding statistical significance between SCC and adenocarcinoma subgroups could be explained by the greater proportion of patients classified as in M1a staging[8] in the SCC

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Table 1. Comparison of the characteristics of the sample by smoking status at chemotherapy initiation.[a]

Characteristic	Smoking cessation prior to chemotherapy		p
	No (n = 47; 48.5%)	Yes (n = 50; 51.5%)	
Gender			
Male	47 (100)	42 (84)	0.006
Female	0 (0)	8 (16)	
Age, years	59 ± 10	60 ± 10	0.324
Histological classification			
Adenocarcinoma	37 (78.7)	37 (74.0)	0.585
Squamous cell carcinoma	10 (21.3)	13 (26.0)	
Staging[b]			
M1a	17 (36.2)	18 (36.0)	0.653
M1b	26 (55.3)	29 (58.0)	0.876
M1c	4 (8.5)	3 (6.0)	0.365
Comorbidities			
Cardiovascular disease	0 (0)	2 (4)	0.495
Diabetes mellitus	5 (10.6)	2 (4)	0.259
Hypertension	9 (19.1)	9 (18)	0.884
Smoking history > 30 pack-years			
No	11 (23.4)	7 (14.0)	0.234
Yes	36 (76.6)	43 (86.0)	
Smoking history, pack-years	51 ± 22	51 ± 21	0.800
Performance status[c]			
0	20 (42.6)	22 (44)	0.800
1	26 (55.3)	26 (52)	
2	0 (0)	1 (2)	
3	1 (2.1)	1 (2)	
Weight loss[d]			
0%	25 (53.2)	30 (60)	0.662
> 5%	16 (34)	15 (30)	
> 10%	6 (12.8)	5 (10)	
Chemotherapy regimen			
Cisplatin plus pemetrexed	20 (42.6)	15 (30)	0.751
Carboplatin plus pemetrexed	13 (27.7)	19 (38)	
Cisplatin plus gemcitabine	3 (6.4)	3 (6)	
Carboplatin plus gemcitabine	5 (10.6)	6 (12)	
Vinorelbine monotherapy	6 (12.8)	4 (14)	

[a]Values expressed as n (%) or mean ± SD. [b]Brierley et al.[7]. [c]Eastern Cooperative Oncology Group performance status scale. [d]Proportion of weight loss within a six-month period.

subgroup than in the adenocarcinoma subgroup. However, the multivariate analysis did not show any influence of metastasis staging on survival in those subgroups. Previous data showed that nicotine inhibits apoptosis induced by systemic therapies in patients with metastatic disease and, consequently, increases resistance to treatment.[9] In addition, nicotine increases tumor growth and neovascularization.[5] Therefore, both exposition to tobacco prior to starting treatment and the interaction of nicotine with chemotherapy might provide possible explanations for smokers having worse prognoses. In our study, the multivariable analysis showed a negative impact of some types of chemotherapy, such as carboplatin plus pemetrexed or monotherapy with oral vinorelbine, on the survival of patients with adenocarcinoma. One possible explanation could be the worse performance status of the patients not treated with cisplatin. In contrast, a previous study showed that the survival of smokers with advanced NSCLC was significantly shorter than that of never smokers, even after adjustment for sensitivity to a specific type of chemotherapy.[10] The multivariate analysis also showed a positive prognostic influence of DM in patients with adenocarcinoma (however, the number of DM patients was low). The effect of DM on patients with NSCLC prognosis remains uncertain, but previous data showed increased survival in patients with DM.[11] We found that a large number of patients in our sample achieved smoking cessation, but only a small proportion of those sought any intensive medical help. The impact of medical advice on smoking behavior might be particularly compelling during cancer treatment, when patients heavily rely on clinicians for support and are generally more motivated to

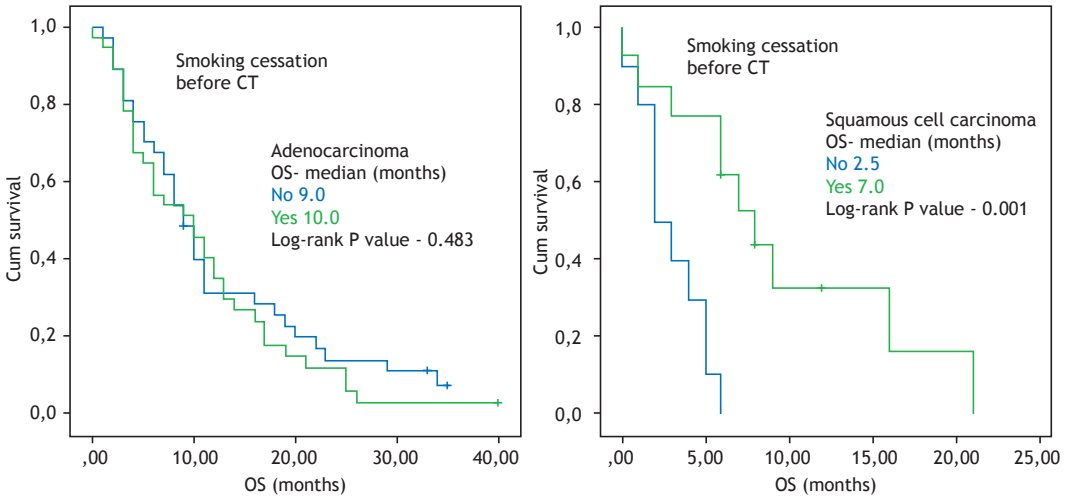

Figure 1. Overall survival (OS) in patients with adenocarcinoma and squamous cell carcinoma according to their smoking status at chemotherapy (CT) initiation. Cum: cumulative.

quit smoking. In a previous study, 65% of smoking patients being treated for lung or head-and-neck cancer reported that they were offered smoking cessation assistance by a medical professional; half of the smokers reported being interested in smoking cessation programs.[12] Physician-based interventions might need to be combined with higher-intensity behavioral and pharmacological interventions to increase long-term smoking cessation among LC patients. The conclusions of our study are tempered by the acknowledgment of the limitations inherent to any retrospective study and by the small sample size. In addition, other factors related to smoking status, such as anxiety levels and quality of life, were not evaluated.

In our sample, smoking cessation was an independent prognostic factor in advanced SCC patients, suggesting that efforts to encourage those patients to quit smoking might be beneficial. Prospective assessments of the determinants of continued smoking in this population is needed to guide effective interventions.

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