Lung Cancer 115 (2018) 109–115

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Characterization of never-smoking and its association with clinical outcomes in Chinese patients with small-cell lung cancer

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ARTICLE INFO

Keywords:
Small-cell lung cancer
Never-smoker
Survival
Prophylactic cranial irradiation

ABSTRACT

Objectives: Small-cell lung cancer (SCLC) has been viewed as a smoking-related disease, with only 2% to 5% patients being never-smokers. This study aimed to investigate the clinical characteristics of never-smoking and its association with treatment outcomes in Chinese SCLC patients in real world.

Methods: We performed a retrospective study of 303 patients with SCLC and grouped into smokers and never-smokers. The clinical characteristics and treatment outcomes of two groups were collected and compared.

Results: In total, 113 patients with limited-stage (LS) SCLC and 190 patients with extensive-stage (ES) SCLC were enrolled. Sixty-nine (22.8%) patients were never-smokers. Both the median progression-free survival (PFS) and overall survival (OS) were significantly longer in never-smokers than in smokers (PFS, 8.37 vs. 7.10 months, $P = 0.036$; OS, 19.73 vs. 14.40 months, $P = 0.044$) in all populations. Multivariate analysis suggested that never-smoking was a significant favorable prognostic factor for PFS (HR = 0.753; $P = 0.047$) instead of OS (HR = 0.780; $P = 0.236$) in patients with SCLC. The objective response rate (ORR) to first-line therapy were similar between two group (52.6% vs. 59.4%, $P = 0.315$). Moreover, prophylactic cranial irradiation (PCI) resulted in marginally significantly longer PFS than observation in patients with ES-SCLC who obtained objective response after first-line therapy (10.57 vs. 7.73 months, $P = 0.075$).

Conclusion: The current study indicated that never-smokers are increasingly prevalent in Chinese patients with SCLC. Never-smokers with SCLC had significantly longer PFS and OS compared with smokers, and smoking was an independent poor prognostic factor for PFS in patients with SCLC.

1. Introduction

Lung cancer is the most common incident cancer and the leading cause of cancer-related death worldwide [1]. Tobacco smoking has been regarded as the most important risk factor for lung cancer. The relationship between smoking and lung cancer is one of the most thoroughly investigated issues in biomedical research, and evidence has been set up since middle of the 20th century to indicate that smoking is the predominant factor for lung cancer [2,3]. Although lung cancer is commonly viewed as a smoker's disease, approximately 10%-15% patients worldwide are never-smokers [4,5]. The prevalence is different geographically and histologically. The proportion of never-smokers in Asian patients is higher than in non-Asian patients [4]. Several studies have shown that small-cell lung cancer (SCLC) is highly associated with smoking among the four major lung cancer histological types [6,7].

Globally, SCLC accounts for 13%-15% of all lung cancers [8]. SCLC is known to be clinically different from non-small cell lung cancer (NSCLC) with a short doubling time, a high growth fraction, and early development of widespread metastases, which contribute to the extremely poor prognosis [8]. Tobacco exposure is strongly associated with the development of SCLC, with only 2% to 5% patients being never-smokers worldwide [9]. With the implementation of strategies for smoking cessation, the incidence of SCLC has been declined in the past decades [10]. It is now well recognized that never-smokers with NSCLC tend to have better survival than smokers [11]. Unlike NSCLC, due to the limited number of cases, there are few prospective and large-scale clinical studies to investigate both the predictive and prognostic relevance of smoking status in patients with SCLC [9,12,13], and no

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https://doi.org/10.1016/j.lungcan.2017.11.022
Received 13 October 2017; Received in revised form 20 November 2017; Accepted 22 November 2017

study was carried out in Chinese population. Therefore, we performed this study to investigate the proportion of never-smokers with SCLC in Chinese population and the effect of smoking history on clinical outcomes in these patients.

In addition, brain metastases remain the common issue in patients with SCLC. Intracranial metastases will eventually occur in more than 50% of patients with SCLC during the course of their disease [14].Previous results from randomized controlled trials and *meta*-analysis have shown that prophylactic cranial irradiation (PCI) could decrease the incidence of brain metastases and bring survival benefit in SCLC populations [15,16]. However, recently a phase III trail drew a different conclusion that PCI did not result in longer overall survival than observation in extensive-stage (ES)-SCLC [17]. Hence, we also evaluated the effect of PCI in the treatment of SCLC patients, especially patients with ES-SCLC in real world.

2. Methods

2.1. Patients inclusion

We performed a retrospective study of 389 patients who were histologically diagnosed with SCLC and treated at the Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University between January 2014 and October 2015. Patients received surgical resection or with missing data on follow-up were excluded in this study. Finally, a total of 303 patients were enrolled. For all the 303 patients, baseline characteristics, comorbidities, treatments and clinical outcomes were extracted from the electronic medical records. Limited-stage (LS)-SCLC is defined as disease confined to a single radiation port with or without mediastinal lymph-node involvement [15]. Extensive-stage (ES) SCLC is regarded as disease that has spread beyond a single radiation port and generally synonymous with distant metastasis. Performance status was assessed for all patients at diagnosis using the Eastern Cooperative Oncology Group Study Performance Status Scale. The presence of comorbidities included one or more of the following conditions: diabetes mellitus, ischemic heart disease, hypertension, asthma, chronic obstructive lung disease, and pulmonary tuberculosis. Never-smokers are defined as those patients who report having smoked $\leq$100 cigarettes in their lifetime. This study was approved by Shanghai Pulmonary Hospital Ethics Committee.

2.2. Statistical analyses

The categorical variables were compared using chi-square test, or Fisher's exact test when needed. The continuous variables were analyzed by ANOVA and Tukey's multiple comparison tests. The Kaplan-Meier Method was used for survival analyses and the log-rank test was used to test for significance. Cox proportional hazards model was used for uni- and multivariate survival analyses to calculate the hazard ratios (HR) and corresponding 95% confidence intervals (CI). Progression-free survival (PFS) was defined as the time from the date of first-line treatment initiation to the date of systemic progression or death and was censored at the date of last tumor assessment (when carried out). OS was calculated from the date of lung cancer diagnosis to death from any cause or was censored at the last follow-up date. Disease progression was defined in accordance with the Response Evaluation Criteria in Solid Tumors guidelines (version 1.1). Statistical analyses were carried out using SPSS 22.0 (IBM Corporation, Armonk, NY, USA). *P* values were two-sided and considered significant if less than 0.05.

3. Results

3.1. Patient characteristics

A total of 303 patients with histologically or cytologically diagnosed SCLC and treated at Shanghai Pulmonary Hospital between January 2014 and October 2015 were enrolled in this study. Of them, 69 (22.8%) patients were never-smokers and 234 (77.2%) cases had a positive history of smoking. Among the 234 smokers, the median smoking amount was 40 pack-years (one pack-year = 20 cigarettes per day during 1 year). The median age at diagnose of smokers was 63 years compared with 60 years of never-smokers ($P = 0.171$). 273 (90.1%) patients were male and 30 (9.9%) were female. Of 30 female patients, never-smokers accounts for 86.7%, while in 273 male cases only 43 (15.8%) patients were never-smokers ($P < 0.001$). As expected, the majority of cases (62.7%) presented with extensive-stage (ES)-SCLC and LS-SCLC accounts for 37.3%. In the perspective of ECOG PS, 300 (99%) patients were evaluated as 0–1 at initial diagnosis, and only 3 (1%) cases were evaluated as > 2. 201 (66.3%) patients had no comorbidities while 102 (33.6%) patients reported with one or more comorbidities. Among the 303 patients, 136 (44.9%) patients received concurrent chemoradiotherapy, 154 (50.8%) received chemotherapy alone and 13 (4.3%) received other therapies. 141 (46.5%) patients received second-line therapy while 162 (53.5%) cases had no second-line treatment records. Except for gender, there was no statistically significantly differences between the groups of never-smokers and smokers with regards to the distributions of baseline characteristics, comorbidities and treatment history. The detailed baseline characteristics and brief summary of treatment are described in Table 1.

3.2. The association of never-smoking with clinical outcomes

The median PFS and OS was 7.33 and 15.50 months in total population. The median PFS and OS were significantly shorter in smokers than in never-smokers (PFS: 7.10 vs. 8.37 months, $P = 0.036$; OS: 14.40 vs. 19.73 months, $P = 0.044$) in all groups (Fig. 1). Among patients with LS-SCLC, the median PFS was shorter in smokers than in never-smokers (7.83 vs. 10.23 months, $P = 0.067$) (Fig. 2A). Similarly,

Table 1
Characteristics and treatment history according to smoking status.

	ALL	Smoker		Never-smoker		*P* value
	N	N	%	N	%	
NO. of patients	303	234	100	69	100	
Age						0.171
Median(range)	63	63		60		
≥65 years	136	110	47.0	26	37.7	
< 65 years	167	124	53.0	43	62.3	
Gender						< 0.001
Male	273	230	98.3	43	62.3	
Female	30	4	1.7	26	37.7	
Stage						0.940
Limited disease	113	87	37.2	26	37.7	
Extensive disease	190	147	62.8	43	62.3	
ECOG PS						0.345
0–1	300	231	98.7	69	100	
2–4	3	3	1.3	0	0	
Comorbidities						0.220
No	201	151	64.5	50	72.5	
Yes	102	83	35.5	19	27.5	
First-line therapy						0.734
Concurrent	136	103	44.0	33	47.8	
Chemotherapy	154	120	51.3	34	49.3	
Other	13	11	4.7	2	2.9	
Second-line therapy						0.161
Yes	141	114	48.7	27	39.1	
No	162	120	51.3	42	60.9	
Response to first-line therapy						
CR + PR	164	123	52.6	41	59.4	
SD	119	94	40.2	25	36.2	
PD	20	17	7.2	3	4.4	
ORR	164	123	52.6	41	59.4	0.315
DCR	283	217	92.8	66	95.6	0.391

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, overall response rate; DCR, disease control rate.