ORIGINAL ARTICLE

Combined Small Cell Carcinoma of the Lung: Is It a Single Entity?

Xiaoliang Zhao, MM,[a,b] Justine N. McCutcheon, BS,[b] Bhaskar Kallakury, MD,[b] Joeffrey J Chahine, MS,[b] Drew Pratt, MD,[c] Mark Raffeld, MD,[c] Yulong Chen, MM,[a] Changli Wang, MD, PhD,[a] Giuseppe Giaccone, MD, PhD[b,*]

[a]*Department of Lung Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin Lung Cancer Center, Tianjin Key Laboratory of Cancer Prevention and Therapy, National Clinical Research Center for Cancer, Tianjin, People's Republic of China*
[b]*Georgetown University, Washington, District of Columbia*
[c]*Department of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

Received 15 August 2017; revised 12 October 2017; accepted 17 October 2017
Available online - 31 October 2017

ABSTRACT

Background: SCLC accounts for 15% and 20% of all lung cancers, with combined SCLC (CSCLC) comprising 2% to 5%. Little is known about the clinical characteristics and molecular changes associated with the various histologic components.

Methods: A total of 205 SCLC cases were resected between 2005 and 2015. Clinical and pathologic features were analyzed. All CSCLC cases were confirmed by histologic examination and immunohistochemistry. The individual components were microdissected using a novel automated dissection system, and DNA was extracted and subjected to targeted exome sequencing.

Results: A total of 10 cases of CSCLC were identified out of 170 cases with adequate histologic material; squamous cell carcinoma comprised the second component in half of these (n = 5). There were no significant differences between CSCLC and pure SCLC with respect to clinical features. The median follow-up time was 36 months. The median survival times of patients with pure SCLC and CSCLC were 58 months and 26 months, respectively ($p = 0.030$). The different components of three cases of CSCLC were deemed adequate for microdissection and sequencing. Approximately 75% of the identified somatic mutations were present in both components. There were also 15 gene mutations or six amplifications unique to only one of the components.

Conclusions: We identified no significant clinical or pathologic differences between pure SCLC and CSCLC; CSCLC was associated with decreased overall survival compared with pure SCLC. The histologic components of CSCLC had high genetic concordance but also showed divergent genotypes. These findings may suggest a common precursor with subsequent acquisition of oncogenic changes in CSCLC.

Keywords: Small cell lung cancer; SCLC; Combined small cell lung cancer; Targeted gene sequencing

Introduction

Lung cancer is the leading cause of cancer death worldwide,[1] with SCLC accounting for approximately 15% to 20% of cases.[2,3] Combined SCLC (CSCLC) is a rare subtype of SCLC, defined by the combination of SCLC and NSCLC components. The NSCLC component is typically composed of adenocarcinoma, squamous cell carcinoma, or large cell carcinoma, but it can also rarely involve sarcomatoid or giant cell carcinoma.[4–6] Furthermore, more than two components can also be observed.

To date, the cell of origin of CSCLC remains unclear and the literature thus far has been based on limited but older techniques such as loss of heterozygosity (LOH), immunophenotype, or comparative genomic hybridization analysis.[7,8] A few studies have concluded that the different components in CSCLC may have a common cellular origin,

*Corresponding author.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Giuseppe Giaccone, MD, PhD, Lombardi Comprehensive Cancer Center, Georgetown University, 3970 Reservoir Rd., Washington, DC 20007. E-mail: gg396@georgetown.edu

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2017.10.010

and that tumor stem cells undergo divergent differentiation during proliferation or, rather, one of the two components arises by random genetic mutations in the other component.[8–10] Exposure to tyrosine kinase inhibitors (TKIs) against the EGFR may lead to the transformation from EGFR-mutant adenocarcinoma to SCLC in less than 10% of EGFR TKI–resistant cases, suggesting plasticity between the different histologic subtypes.[11] An increase in CSCLC after neoadjuvant chemotherapy has been observed and is thought to be due to a positive selection of NSCLC by chemotherapy.[12,13] Alternatively, CSCLC could represent the synchronous apposition of two malignant tumors (collision tumor).[14]

The prevalence of CSCLC is variable, being reported in 2% to 28% of all SCLC cases.[15] This variation may reflect ongoing changes in the classification of SCLC, as well as the nature of the specimen obtained (e.g., resection versus small biopsy versus fine-needle aspiration specimen). There are few studies assessing the clinical and prognostic features of CSCLC after surgery. Furthermore, few studies have addressed the molecular changes in the different histologic components. Here, we have investigated the clinicopathologic features of a large series of resected SCLCs and performed next-generation sequencing (NGS) on the different components in three CSCLC cases.

Materials and Methods

This study included a total of 170 patients with resected SCLC at the Tianjin Medical University Cancer Institute and Hospital between 2005 and 2015 for which adequate material was available. Details of this series are described elsewhere (X. Zhao, Tianjin Medical University Cancer Institute and Hospital, personal/written communication, 2017). All specimens were reviewed and independently confirmed by two board-certified pathologists. Ten cases of CSCLC were identified, accounting for 5.9% of the SCLC in this series (Table 1). All cases were restaged according to the seventh edition of American Joint Committee on Cancer TNM staging system for lung cancer.[16] Clinical data on all patients were extracted from medical records and follow-up (as of March 2017) was obtained. Overall survival (OS) was defined as the interval between the date of the operation and the time of death or the date of the last follow-up.

Immunohistochemistry

All samples were formalin-fixed and paraffin-embedded (FFPE); 4-μm tissue sections were stained with hematoxylin and eosin (HE) and analyzed using a select panel of immunohistochemical (IHC) markers. Pretreatment of the FFPE sections with heat-induced epitope retrieval was performed. Optimal results were obtained by pretreating tissues with heat-induced epitope retrieval using diluted Envision FLEX Target Retrieval Solution, HIGH pH (50×) (Agilent Technologies, Santa Clara, CA). Deparaffinization, rehydration, and epitope retrieval were performed in DAKO PT Link (PT100/PT101) (Agilent Technologies). The following parameters were used for PT Link: preheat temperature, 65°C; epitope retrieval temperature and time, 97°C for 20 minutes; and cool down to 65°C. Racks were placed in diluted Envision Flex Wash Buffer (20×) (Agilent Technologies) for 5 minutes.

Slides were treated with Flex Peroxidase Blocking solution for 5 minutes and then with the first antibody with an incubation time of 20 minutes, Flex Mouse Linker for 15 minutes, Flex HRP for 20 minutes, Flex DAB with Substrate-Chromogen for 10 minutes, and Flex hematoxylin for 5 minutes. Wash buffer was applied before the addition of each reagent for 5 minutes to guarantee that no residual remains of any reagent were left on the slide.

All the antibodies were run on the Dako/Agilent Autostainers Link 48, and the antigen retrieval for all the antibodies was performed on the Dako/Agilent PT Links.

Table 1. Clinicopathologic Characteristics of CSCLC (n = 10)

Case	Age	Sex	Smoking index	Location	pStage	Surgery Type	R Resection	Diameter, cm	Adjuvant chemotherapy
1	74	M	0	RL	IA	Wedge	R1	2	Yes
2	63	M	1600	RL	IIA	Lobectomy	R0	7	Yes
3	70	F	0	RM	IV	Lobectomy	R0	6	No
4	59	M	1200	LU	IIIA	Lobectomy	R0	5	Yes
5	63	M	3200	RL	IA	Lobectomy	R0	2	Yes
6	60	M	800	LU	IA	Lobectomy	R0	2	No
7	62	M	800	LU	IIIA	Wedge	R1	2.2	No
8	58	M	1200	LL	IIIA	Lobectomy	R0	3	Yes
9	44	M	40	RL	IIIA	Lobectomy	R0	5	Yes
10	49	M	400	LU	IIIB	Lobectomy	R0	3.5	No

Note: Smoking index is cigarettes per day multiplied by years smoked.
CSCLC, combined SCLC; M, male; F, female; LLL, left lower lobe; RLL, right lower lobe; RUL, right upper lobe; LUL, left upper lobe; RML, right middle lobe.