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Non-small cell lung cancer transdifferentiation into small cell lung cancer: A case series

Tahreem Ahmed[a], Macarena R. Vial[b], David Ost[c], John Stewart[d], Muhammad A. Hasan[c], Horiana B. Grosu[c,*]

[a] Departments of Thoracic Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[b] Department of Pulmonary Medicine, Clinica Alemana de Santiago-Universidad del Desarrollo, Chile
[c] Departments of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
[d] Departments of Cytopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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ABSTRACT

Transdifferentiation from non-small cell lung cancer (NSCLC) to small cell lung cancer (SCLC) has been reported mostly in adenocarcinomas and has been described as a cause of acquired tyrosine kinase inhibitor (TKI) resistance. However, transdifferentiation has also been described in patients with different histologic characteristics and patients not exposed to TKIs and with no epidermal growth factor receptor (EGFR) mutation (the target of TKIs). To this date transdifferentiation remains poorly understood.

We conducted a retrospective case series of patients who had biopsy-proven SCLC within 2 years after a diagnosis of NSCLC or in the same location as the known primary NSCLC.

We found that 0.2% of lung cancer patients at our institution experienced transdifferentiation. Among these, 30 had adenocarcinoma and 16 had squamous cell carcinoma. In 27 of the 30 patients with adenocarcinoma (90%), SCLC was found in the same location as the known primary. In 14 of the 30 patients (47%), SCLC occurred within 2 years after the NSCLC diagnosis. In 12 of the 16 patients with squamous cell carcinoma (75%), SCLC was found in the same location as the known primary. In 8 of these 16 patients (50%), SCLC occurred within 2 years after the NSCLC diagnosis. Few patients with adenocarcinoma and none with squamous cell carcinoma were treated with TKIs or had an EGFR mutation.

In conclusion the findings in the current study suggest that the discovery of SCLC histology after treatment of NSCLC may be more common than thought suggesting that further study is warranted to evaluate the phenomenon of transdifferentiation.

1. Introduction

Lung cancer is considered one of the leading causes of death due to cancer worldwide [1]. The classification of lung cancer is based on histologic characteristics, and it is mainly divided into two subtypes: non-small cell lung cancer (NSCLC), which is responsible for 85% of lung cancer cases, and small cell lung cancer (SCLC) [1]. NSCLC is further subdivided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [1,2]. Although most lung cancers are classified as either NSCLC or SCLC and probably remain as such, the development of safer biopsy methods has allowed more frequent repeat biopsies, which sometimes reveal changing histologic characteristics. These inconsistent histologic findings could be explained by tumor heterogeneity but may also represent transdifferentiation from one histologic type to another.

The phenomenon of transdifferentiation is poorly understood, but transdifferentiation from NSCLC to SCLC has been reported mostly in adenocarcinomas and has been described as a cause of acquired resistance to tyrosine kinase inhibitors (TKIs), which target epidermal growth factor receptor (EGFR), in up to 5–14% of patients receiving TKIs [3–9]. However, transdifferentiation has also been described in patients not exposed to TKIs and with no EGFR mutation.

We performed a retrospective case series to describe the clinical characteristics and prognosis of patients who presented with transdifferentiation from NSCLC to SCLC at our institution. These preliminary data are meant to inform future studies of transdifferentiation from NSCLC to SCLC to help improve understanding of the phenomenon.

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor

* Corresponding author at: Department of Pulmonary Medicine, Unit 1462, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA.
E-mail address: hbgrosu@mdanderson.org (H.B. Grosu).

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2. Patients and methods

2.1. Patients

We retrospectively reviewed the pathology records of patients who visited our institution from January 2003 through January 2015 who were diagnosed with both SCLC and NSCLC. Approval was obtained from the Institutional Review Board committee, protocol number PA16-1070. Patients aged 18 years or older were included. In addition to the pathologic findings, we collected patient demographic information, disease stage, EGFR status, treatment history, and survival status. The diagnosis of NSCLC and SCLC was confirmed through histologic and immunohistochemical testing (chromogranin, synaptophysin, CD56, and MIB1).

2.2. Transdifferentiation definition

NSCLC transdifferentiation into SCLC was defined as a finding of biopsy-proven SCLC occurring within 2 years after a diagnosis of NSCLC. If SCLC was diagnosed more than 2 years after NSCLC was diagnosed, this was considered transdifferentiation only if the SCLC was found in the same location as the known primary NSCLC. Same location was defined as cancer in the same exact area of the primary malignancy (i.e. NSCLC was in a mass in the anterior segment of right upper lobe, SCLC was in same mass in the anterior segment of right upper lobe).

2.3. Statistical methods

For demographic and clinical characteristics, we used mean and standard deviation to describe continuous variables distributed normally. We used medians and interquartile ranges for non-normally distributed data and frequencies for categorical data. For time-to-event outcomes (i.e., overall survival), we used the Kaplan–Meier product-limit estimator. We accepted a two-tailed p-value of < 0.05 as statistically significant for all analyses. We used Intercooled Stata 13 software (College Station, TX) for all analyses.

3. Results

We reviewed 23,015 consecutive cases from the period studied and found 502 patients diagnosed with both NSCLC and SCLC. Forty-six of 502 met the definition of transdifferentiation; hence transdifferentiation was found in 0.2% of patients during the period studied. At the time of initial diagnosis, 30 of the 502 patients (6%) had adenocarcinoma and 16 (3%) had squamous cell carcinoma.

In 27 of the 30 patients with adenocarcinoma (90%), SCLC was found in the same location as the known primary. In 14 of these 30 (47%) patients, SCLC was diagnosed within 2 years after the NSCLC diagnosis, while the patients were considered to have active disease. In 16 of these patients (53%), SCLC was diagnosed 2 years after the NSCLC diagnosis, and the median time to diagnosis was 36 months, range 25 month–41 months.

Eight patients in the adenocarcinoma group were treated with TKIs, although EGFR status was evaluated in only six patients and a mutation detected in four patients.

In 12 of the 16 patients with squamous cell carcinoma (75%), SCLC was found in the same location as the known primary. In 8 of these 16 patients (50%), SCLC was diagnosed within 2 years after the NSCLC diagnosis, while the patients were considered to have active disease. In 8 of these 16 patients (50%), SCLC was diagnosed a 2 years after the NSCLC diagnosis, and the median time to diagnosis was 32 months, and ranged from 28 month to 36 months. No patients in the squamous cell carcinoma group were treated with TKIs, although EGFR status was evaluated in one patient, and no mutation was detected. Clinical characteristics by histologic type are shown in Table 1.

In all patients with adenocarcinoma and squamous cell carcinoma, the reason for repeat biopsy was disease progression. In patients with adenocarcinoma (n = 30), the repeat biopsy was performed as follows: 13 fine-needle aspirations, 15 core biopsies, and 2 surgical biopsies. In patients with squamous cell carcinoma (n = 16), the repeat biopsy was performed as follows: 13 fine needle aspirations, 2 core biopsies, and 1 surgical biopsy.

More patients with squamous cell carcinoma had stage III–IV disease than those with adenocarcinoma. Overall survival from the time of diagnosis of SCLC was poor, with a median of 304 days (interquartile range, 93–621 days). Overall survival did not differ between those diagnosed with adenocarcinoma and those diagnosed with squamous cell carcinoma ($p = 0.318$).

4. Discussion

This retrospective case series of lung cancer patients with overlapping histologic characteristics of NSCLC and SCLC covered a period of 12 years at our institution. Transdifferentiation was seen in 46 patients (0.2%), in both adenocarcinoma and squamous cell carcinoma. This observation indicates that transdifferentiation can occur across histologic types and may suggest that transdifferentiation can occur independently of EGFR mutation status.

EGFR-mutant adenocarcinomas are usually found in young adults and nonsmokers; in contrast, SCLC and squamous cell carcinomas are related to smoking. Effective molecularly targeted therapies have disproportionately impacted adenocarcinomas over squamous cell carcinomas, as well as never or light smokers over heavy smokers, likely because EGFR positivity is found more commonly in patients with adenocarcinoma than in patients with squamous cell carcinoma [7,10–13]. However, our findings suggest that transdifferentiation to SCLC may not be solely related to the presence of mutant EGFR.

The findings in the current study are similar to those reported in a case series written before the discovery of EGFR-activating mutations. In that study, among patients originally diagnosed with NSCLC who developed resistance to conventional chemotherapy or radiotherapy, about 5% were found to have SCLC at the time of relapse [14]. Another series described two patients with adenocarcinoma that transformed into SCLC, in tumors that did not have EGFR driver mutations [15].

The phenomenon of transdifferentiation also occurs in prostate cancers. In prostate cancer, neuroendocrine differentiation of adenocarcinoma is correlated with disease progression and response to androgen deprivation therapy. Thus, neuroendocrine differentiation may represent a mechanism of treatment resistance in prostate cancer [16,17]. This suggests that transdifferentiation may lead to treatment resistance rather than arise as a result of exposure to targeted therapy.

The findings in the current study are subject to scrutiny given that lung cancers with combined histologic characteristics are known to exist, and SCLC with a large-cell component has been observed in about 10% of cases of SCLC [18,19]. This was investigated in two large case series, which showed that 2–10% of SCLCs had an NSCLC component present [14,20]. Transdifferentiation from NSCLC to SCLC is one possible explanation for these results. However, another possible explanation is that insufficient pathologic material was collected from the core biopsy samples or needle aspirates to determine whether combined histologic characteristics were present at the initial diagnosis. The question of combined histologic characteristics or transdifferentiation is very important when it comes to treatment decisions, especially when tumors do not respond as initially expected or two or more different lesions show discordant responses. In these cases, a repeat biopsy may be indicated.

Our study has some limitations. First, it is a retrospective study of a single-center database. Second, EGFR mutation status was tested in only a few patients. The lack of genotyping is a major limitation in our study and it is also possible that patients identified from the pathology database had synchronous tumors or tumors with combined histologic characteristics rather than true transdifferentiation. Larger studies will

Table 1
Patient characteristics by histologic type.

Characteristic	No. (%)[a]	
	Adenocarcinoma, n = 30	Squamous cell carcinoma, n = 16
Mean age ± standard deviation	63.25 ± 11.88 years	67.95 ± 6.98 years
Sex		
Female	17 (57)	5 (31)
Male	13 (43)	11 (69)
Race/ethnicity		
White	26 (87)	16 (100)
Black	1 (3)	0 (0)
Hispanic	0	0 (0)
Asian	3 (10)	0 (0)
Smoking status		
Current	14 (47)	6 (38)
Never	5 (17)	1 (6)
Prior	11 (37)	9 (56)
Stage at diagnosis		
IA	8 (27)	2 (13)
IB	3 (10)	3 (19)
IIA	1 (3)	1 (6)
IIB	4 (13)	0 (0)
IIIA	8 (27)	1 (6)
IIIB	0 (0)	6 (38)
IV	6 (20)	3 (19)
Active disease at the time of small cell lung cancer diagnosis		
Yes	14 (47)	8 (50)
Small cell lung cancer diagnosed in same region as primary malignancy		
Yes	27 (90)	12 (75)
EGFR[b] status evaluated		
Yes	6 (20)	1 (6)
EGFR mutation detected		
Yes	4 (67)	0 (0)
Patient received surgery		
Yes	12 (40)	5 (31)
Patient received radiation		
Yes	21 (70)	10 (63)
Patient received platinum-based chemotherapy		
Yes	15 (50)	10 (63)
Patient was treated with tyrosine kinase inhibitors		
Yes	8 (27)	0 (0)
Final outcome		
Alive	13 (43)	2 (13)
Dead	17 (57)	13 (81)
Lost to follow-up	0 (0)	1 (6)

[a] Percentages may not add up to 100 owing to rounding.
[b] EGFR indicates epidermal growth factor receptor.

be needed to identify the precise frequencies of SCLC transdifferentiation in EGFR-mutant and non-mutant NSCLC.

Nevertheless, the findings in the current study suggest that the discovery of SCLC histology after treatment of NSCL may be more common than thought suggesting that further studies are warranted to evaluate the phenomenon of transdifferentiation.

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Conflict of interest

The authors have no conflict of interest to disclose.

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