Small-Cell Lung Cancers in Patients Who Never Smoked Cigarettes

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Introduction: We describe clinical, pathologic, and molecular characteristics of never-smoker patients with small-cell lung cancers (SCLCs).

Methods: We identified cases of SCLCs evaluated at our institution from 2005 to 2012. We collected smoking history, demographic, treatment, and survival data. *EGFR*, *KRAS*, *PIK3CA*, *ALK* testing, RB protein expression, and next generation sequencing were performed on available samples.

Results: Two percent (23 of 1040) of patients with SCLCs were never-smokers. Eighty-three percent (19 of 23) had de novo SCLCs, whereas 17% had SCLC transformation as acquired resistance to erlotinib after treatment for *EGFR*-mutant lung carcinomas. Median survival from SCLC diagnosis was 23 months. Of de novo SCLCs, *ALK* rearrangement, *KRAS* mutations, *EGFR* mutations, and RB loss were identified in zero of five, zero of eight, two of eight, and six of seven, respectively. Two de novo samples underwent next generation sequencing. One had mutations in *p53* and *RB1* with amplification in *TERT*, and a second had mutations in *CBL* and *GNAS* with amplification in *MYCL1*.

Conclusions: Two percent of patients with SCLCs are never-smokers. Although transformation to SCLC can rarely occur in acquired resistance to erlotinib, 83% of never-smokers with SCLCs had de novo SCLC. RB loss was noted in 86% of cases. Multiplexed genotyping can be performed on tissues to identify potentially actionable oncogenic drivers.

Key Words: Small-cell lung cancer, Never-smokers

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Although tobacco smoking remains the most important risk factor for the development of small-cell lung cancer (SCLC), an epidemiologic study reported that 3% of patients with SCLCs are never-smokers.[1] Several reports describe the rare, but well-documented, phenomenon of transformation to SCLC as a mechanism of acquired resistance (AR) to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in 4 to 14% of patients initially treated for *EGFR*-mutant lung adenocarcinomas, including in some patients who are never-smokers.[2–5]

Scant literature exists describing de novo SCLCs among patients who are never-smokers. We report on 23 patients with SCLCs who classify themselves as never-smokers.

MATERIALS AND METHODS

Patient Identification and Smoking History Documentation

We performed a retrospective review of 1040 SCLC patients evaluated at Memorial Sloan-Kettering Cancer Center between 2005 and 2012. Patients with lung cancers assessed at Memorial Sloan-Kettering Cancer Center complete a prospective, self-administered smoking questionnaire at the initial visit. Never-smokers are defined as those patients who report having smoked ≤100 cigarettes in their lifetime.

Pathologic Review of SCLC

The diagnosis of SCLC was confirmed through histologic and immunohistochemical (IHC) testing (chromogranin, synaptophysin, CD56, and MIB1) by a thoracic pathologist.

KRAS, EGFR, ALK, and RB Testing

Patients with sufficient tissue underwent testing for *EGFR* and *KRAS* mutations and *ALK* rearrangements. *EGFR* mutations (exon 19 deletions and exon 21 L858R amino acid substitutions) were identified by mutation-specific PCR-based methods.[6–8] *KRAS* codons 12 and 13 mutation identification was performed by both mass spectrometry (Sequenom, Inc., San Diego, CA)-based genotyping and direct sequencing. *ALK* rearrangements were tested using either fluorescence in situ hybridization (dual-color break-apart ALK probe, Abbott Molecular, Abbott Park, IL) or IHC (ALK-01 Ventana 790–2918). RB expression was analyzed using IHC (clone 1F8, Leica Biosystems, Buffalo Grove, IL).

Comprehensive, Integrated Mutation Analysis of Actionable Cancer Genes Using Next Generation Sequencing (NGS)

DNA was extracted from biopsied tissue and cytology specimens (and patient-matched normal tissue) using Qiagen nucleic acid extraction kits. Using our MSK-IMPACT (integrated mutation profiling of actionable cancer targets) assay, bar-coded sequence libraries were prepared (Illumina TruSeq), and exon capture was performed on bar-coded pools by hybridization (Agilent SureSelect Target Enrichment) using custom oligonucleotides to capture all exons and select introns of 279 cancer genes. DNA was sequenced on an Illumina HiSeq 2000 to maximize sensitivity for detecting mutations. This strategy enables the identification of mutations, indels, and copy number alterations involving these 279 genes.

RESULTS

Incidence

Two percent of patients (23 of 1040) with SCLCs were never-smokers. Among never-smokers with SCLCs, 83% (19 of 23) had de novo SCLCs, and 17% (4 of 23) of patients had small-cell transformation as a mechanism of AR to EGFR TKIs in *EGFR*-mutant lung adenocarcinoma. Baseline characteristics are listed in Table 1. Clinical and pathologic characteristics of each patient are listed in Table 2.

de novo SCLC

Pathologic characteristics

Pathologic rereview confirmed the following: 15 pure SCLC; one mixed SCLC and large cell neuroendocrine carcinoma; one SCLC and spindle and giant cell carcinoma (Figs 1*A*, 1*B*); and two mixed SCLC and adenocarcinoma.

TABLE 1. Clinical Characteristics of Patients with Small-Cell Lung Cancer (SCLC) Who Are Never-Smokers

	SCLC as Acquired Resistance (n = 4)‡	de novo SCLC (n = 19)
Sex		
Male	0	9
Female	4	10
Median age at diagnosis (range)	48 (42–75)*	65 (35–94)
Race		
White	2	13
Black	0	3
Asian	2	3
Stage at diagnosis		
Limited	0	5
Extensive	4	14
Brain metastases at presentation		
Yes	2	4
No	2	15

‡All four of these patients had been treated with erlotinib.
*For patients with SCLC transformation as a mechanism of acquired resistance to EGFR TKIs, median age at diagnosis is the age at which SCLC transformation was diagnosed.

Clinical characteristics

Of 19 patients with de novo SCLCs, 5 were either lost to follow-up or had inadequate information available regarding treatment course and response. Of the 14 cases with available treatment history, all received first-line etoposide/platinum doublets. Fifty-seven percent of these patients (8 of 14) had a response to chemotherapy that lasted ≥3 months from completion of first-line therapy. Median time to progression was 11 months (95% CI: 5–13 months). Median overall survival (OS) from the time of SCLC diagnosis was 23 months (95% CI: 10–27 months).

EGFR, KRAS, ALK, and RB Testing

Of the 19 de novo SCLC cases, 8 underwent testing for *EGFR* Exon 19 deletion and Exon 21 L858R mutation. An *EGFR* L858R mutation was found in one patient, whose tumor contained SCLC and adenocarcinoma components. This patient initially received erlotinib, carboplatin, and etoposide, with progression of disease within three months of completing chemotherapy. Although he continued erlotinib throughout his subsequent chemotherapeutic regimens, his disease rapidly progressed. The tumor of one patient with pure SCLC harbored an *EGFR* Exon 19 deletion and *PIK3CA* E545K mutation. This patient had progressive disease after four cycles of etoposide/platinum. He was then initiated on erlotinib, with progression of disease after just 4 weeks of therapy.

There were no *KRAS* mutations or *ALK* rearrangements identified in the cases tested for these alterations. Six of seven cases tested for RB expression demonstrated RB loss (Table 3).

Acquired Resistance SCLC

Pathologic characteristics

Of the four patients with SCLC as a mechanism of AR to EGFR TKIs, two had pure SCLC, one had mixed histology of SCLC and adenocarcinoma, and one had SCLC, adenocarcinoma, and large cell neuroendocrine carcinoma components.

Clinical characteristics

All four patients were women (median 48 years; range 40–75 years) at the diagnosis of SCLC transformation from *EGFR*-mutant lung adenocarcinoma. Once the diagnosis of SCLC was made, two patients received platinum/etoposide. One of these patients underwent local therapy with surgical resection of a lung nodule that demonstrated recurrent growth, although all other sites of disease had resolved.[9] Pathology review of this specimen with acquired resistance demonstrated SCLC, adenocarcinoma, and large cell neuroendocrine carcinoma components. After receiving six cycles of adjuvant carboplatin, etoposide, and erlotinib therapy, this patient had a nine-month, disease-free interval after treatment. The two patients who did not receive platinum/etoposide therapy had varied treatments and clinical courses.