Somatic STK11 and Concomitant STK11/KRAS MutationalFrequency in Stage IV Lung Adenocarcinoma Adrenal Metastases

Ferga C. Gleeson, MD,* Benjamin R. Kipp, PhD,† Michael J. Levy, MD,* Jesse S. Voss, CT(ASCP),† Michael B. Campion, † Douglas M. Minot, CT(ASCP), † Zheng J. Tu, PhD,‡ Eric W. Klee, PhD,‡ Konstantinos N. Lazaridis, MD,*§ and Sarah E. Kerr, MD†

Abstract: Somatic serine/threonine kinase 11 (STK11) also known as liver kinase B1 (LKB1) is a tumor suppressor gene and ranks as the third most frequently mutated gene in lung adenocarcinoma. However, current molecular testing guidelines recommend evaluating for epidermal growth factor receptor mutations and ALK fusions to guide therapy in all patients with advanced stage adenocarcinoma, regardless of gender, race, or smoking history. Identifying alternative “driver” mutations and using actionable targeted pharmacotherapy is a key approach to providing effective individualized medical care. The analytical sensitivity and parallel multigene approach of targeted next-generation sequencing is an attractive methodology for use for cytology specimens. The presented lung adenocarcinoma study revealed that STK11 mutations alone and concomitant KRAS/STK11 mutations were identified in 18.2% and 4.5% of solitary adrenal metastases, respectively. Molecular profiling of epidermal growth factor receptor tyrosine kinase inhibitor resistant tumors may help to identify patients who would most benefit from alternative single or dual pathway inhibition potentially leading to a revision in current molecular testing guidelines.

Key Words: Lung adenocarcinoma, Adrenal metastasis, Cytology, Multigene profile, Targeted therapy.

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KRAS, ALK, BRAF, and epidermal growth factor receptor (EGFR) are oncogenic alterations found in 50% of lung adenocarcinomas. Some tumors with EGFR mutations or ALK gene rearrangements are responsive to targeted therapy, whereas KRAS and BRAF mutations predict resistance to such therapies. The ability to individualize therapies based on genetic testing of tumors represents significant progress. Other gene rearrangements (ROS1 and RET) have been identified as therapeutic targets in lung cancer, but are rare events. Little emphasis has been placed on mutated tumor suppressor genes. The Tumor Sequencing Project identified 26 significantly mutated oncogenes and tumor suppressor genes. The most frequently identified tumor suppressor genes were TP53 (70%), STK11 (18%), and CDKN2A (5%).

STK11 encodes the serine/threonine protein kinase and is part of the STK11/AMPK/mTOR signaling pathway. It has been identified in the histological spectrum of sporadic adenocarcinoma, squamous cell, and large-cell carcinoma of the lung. It has been identified in up to 33% of primary lung adenocarcinomas and 12% of brain metastases. Patients with concomitant KRAS/STK11 mutations have a poorer prognosis when compared with patients with KRAS-mutated but STK11 wild-type adenocarcinoma, suggesting that loss of STK11 induces a more aggressive tumor phenotype. The loss of STK11 in melanoma and cervical cancer promotes widespread and high-grade metastasis. In murine models, STK11-deficient tumors demonstrated more frequent metastasis when compared with tumors with TP53 alterations.

Concomitant STK11/KRAS mutant non–small-cell lung cancer cell lines are sensitive to dual threonine and tyrosine recognition kinase (MEK) inhibitors and may be suitable for mTOR-targeted therapies. Phenformin, a mitochondrial inhibitor and analog of metformin, has also been proposed as a cancer metabolism–based therapeutic strategy to selectively target STK11-mutated tumors. Furthermore, deoxythymidylate kinase is an additional potential therapeutic target for STK11 mutant tumors.

We have previously published our experience with optimal fine-needle aspirate and touch preparation smear cellularity characteristics for successful theranostic next-generation sequencing and the presented patients represent an unpublished subset of that data. In cytologically proven adrenal metastasis from patients with treatment-naïve lung adenocarcinoma, we aimed to identify the prevalence of STK11 mutant status and concomitant STK11/KRAS mutant status with a targeted next-generation sequencing-based approach using a 50-gene cancer hotspot panel.
MATERIALS AND METHODS

Twenty-two adrenal gland cytology specimens representing a solitary metastatic site from lung adenocarcinoma obtained either by endoscopic ultrasound fine-needle aspiration or computed tomography guidance fulfilled cytology smear selection and DNA quality criteria. Subsequently, multiplex polymerase chain reaction was performed by amplifying 30 ng of DNA with the Ion AmpliSeq Cancer Hotspot Panel v2 and the Ion AmpliSeq Library Kit 2.0 (Life Technologies, Carlsbad, CA) per manufacturer’s instructions. This AmpliSeq kit targets 207 amplicons (>2800 potential mutations) within 50 cancer-associated genes, including: ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNAQ, GNAS, GNA11, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCBI, SMO, SRC, STK11, TP53, and VHL (Supplemental Digital Content, http://links.lww.com/JTO/A731).

RESULTS

Patient Characteristics

The treatment naïve adenocarcinoma patient cohort was comprised of 12 men and 10 women (age, 69.9 ± 11.2 years) and they were followed for 10.6 months (interquartile range [IQR], 6.6–20.8) after cytologic diagnosis of adrenal metastasis. This group included current smokers (n = 14 [77.8%] with a 50-year pack history [IQR, 30–68]), former smokers (n = 6 [27.3%] with a 30-year pack history [IQR, 7.5–35]), and never smokers (n = 2 [11%]). Overall mortality (n = 18 [81.9%]) was observed at 9.2 months (IQR, 3.4–12.9) after diagnosis.

Cytology Mutation Profiling

Subsequent review identified 27 pathogenic alterations in eight of the 50 tested genes. Pathogenic alterations were identified in 19 (86.4%) of 22 patients, with a median of 1 (1–2) alteration per patient. Specific pathogenic alterations and respective frequencies are presented in Table 1. Four (18.2%) patients’ tumors possessed STK11 mutations (Table 2). Concomitant KRAS/STK11 mutations were identified in one patient (4.5%). EGFR and KRAS pathogenic alterations were mutually exclusive. There was no difference in age, gender, smoking status, or disease-related mortality, between STK11 mutant and STK11 wild-type adenocarcinoma patients (Table 3).

Exploring Customized Genotype/Directed Therapy

EGFR mutations were identified in two patients (11%), making them eligible for EGFR-tyrosine kinase inhibitor (TKI) therapy. All four STK11 mutant patients were EGFR, TP53, RB1, and PTEN, N = 1 (4.5%)

Overall survival (mo) 8.4 22.7 22.7 2.6


Bold indicates the gene mutations identified.
CDKN2A, BRAF, PTPN11, ERBB2, NRAS, CTNNB1, AKT1, and MEK wild type. Standard EGFR-TKI therapy is predicted to have limited therapeutic value for this mutational profile.

DISCUSSION

In clinical practice, it is critical to accurately define patients with tumor phenotype subpopulations that are most likely to benefit from pharmacologic intervention. EGFR and ALK testing has become essential in the treatment of patients with advanced non–small-cell lung cancer, present in up to 50% of Asian lung adenocarcinomas populations in contrast to only 5% to 15% in a non-Asian population. This underscores the need to search for other “druggable” mutations or concomitant mutations to develop new target opportunities. STK11 ranks as the third most frequently mutated gene in lung adenocarcinoma, following TP53 and KRAS. The presented study revealed that STK11 mutations and concomitant KRAS/STK11 mutations were identified in 18.2% and 4.5% of solitary adrenal adenoma, following TP53 and KRAS. The STK11 mutation frequency is concordant with the results of the Tumor Sequencing Project. Due to the relative high frequency of STK11 mutations and involvement of STK11 in the mTOR signaling pathway, this presents a potential opportunity for development of new targeted therapy. If managed solely with cytotoxic chemotherapy, even isolated adrenal metastases progress to death with reported survival of only 6 to 9 months. By using a multigene cancer sequenced analysis, a potential opportunity for development of new targeted therapy presents a potential opportunity for development of new targeted therapy.

TABLE 3. Correlation of STK11 Mutations with Clinicopathologic Characteristics and with EGFR, KRAS, or TP53 Mutations

<table>
<thead>
<tr>
<th>STK11 Mutant (n = 4)</th>
<th>STK11 Wild Type (n = 18)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td>74.6±9.9</td>
<td>68.8±11.4</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>2 (50%)</td>
<td>10 (55.6%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3 (75%)</td>
<td>11 (61.1%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1 (25%)</td>
<td>5 (27.8%)</td>
</tr>
<tr>
<td>Bilateral adrenal disease</td>
<td>1 (35%)</td>
<td>1 (35%)</td>
</tr>
<tr>
<td>Disease-related mortality</td>
<td>4 (100%)</td>
<td>14 (77.8%)</td>
</tr>
<tr>
<td>Overall survival months</td>
<td>7.5 (2.6–22.7)</td>
<td>12.3 (1.1–71.0)</td>
</tr>
<tr>
<td>Mutational profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS mutation</td>
<td>1 (25%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>0</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>0</td>
<td>10 (55.6%)</td>
</tr>
<tr>
<td>RET mutation</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>PTEN mutation</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>GNAS mutation</td>
<td>0</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>PIK3CA mutation</td>
<td>0</td>
<td>1 (5.6%)</td>
</tr>
</tbody>
</table>

All patients were RB1, CDKN2A, BRAF, PTPN11, ERBB2, NRAS, CTNNB1, AKT1, and MEK wild type.

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REFERENCES


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**Erratum**

Early-Stage Lung Cancer: 40s Anniversary: Erratum

The title of the article beginning on page 1434 of the October 2014 issue appeared incorrectly as Early-Stage Lung Cancer: 40s Anniversary. The correct title for this article is Early Stage Lung Cancer: Progress in the Last 40 Years.

Reference: